THE SYNTHESIS OF CHEMOTHERAPEUTIC AGENTS

DERIVED FROM

p-PHENANTHROLINE AND BENZTHIAZOLE

by

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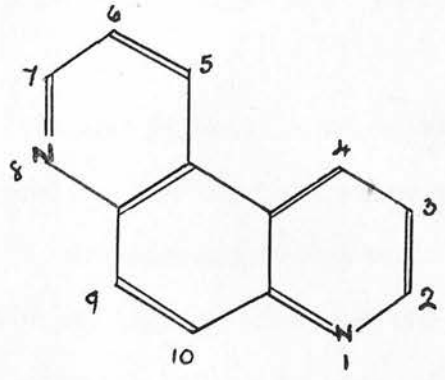
Nomenclature and Numbering.

p-Phenanthroline Derivatives.

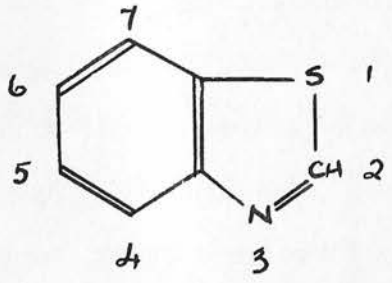
The numbering of the p-phenanthroline nucleus used throughout this thesis is shown below.



This structure has also been described as 5:6:3':2'-pyridoquinoline, but the name p-phenanthroline is preferred unless it is desired to emphasise the relation to the quinoline nucleus.

Benzthiazole Derivatives.

The numbering of the benzthiazole nucleus used in this thesis is as under.



All new compounds which have been analysed or of which derivatives have been analysed are underlined wherever they appear in the text.

I. INTRODUCTION AND GENERAL SURVEY OF THE LITERATURE

In general terms the object of this research was to synthesise chemotherapeutic agents. More particularly, the aim was to investigate the possible chemotherapeutic activity of certain compounds against the malarial parasite. It is of interest therefore to consider the disease, its nature and control.

In distribtuion, malaria is world-wide, being found in almost every country. It has been estimated that several hundred million people are stricken with the disease each year, of whom about three million die. In the recent world war much fighting took place in malarious areas and heavy temporary casualties were inflicted on the fighting personnel by tropical disease, principally malaria. This situation was serious enough at the time but no less dangerous is the result today for this country and, especially, the United States, by the return of many of these "cured" soldiers who still harbour the malarial parasite in their blood-streams. Much research has been done on the problem and results, although not the complete answer, have been obtained.

To appreciate the problem, it is necessary to consider first the life cycles of the malaria parasites of which there are three common species infective to man, Plasmodium vivax, which causes benign tertian malaria, Plasmodium falciparum, which causes the malignant form, and Plasmodium malariae,

which causes quartan malaria. The cycles of the three plasmodia, all essentially the same, are biphasal, there being an asexual existence in the blood-stream of certain vertebrates and a sexual development in the anopheles mosquito, shown by Ross in 1898. When man is bitten by an infective mosquito, sporozoites from the salivary glands of the mosquito enter the blood stream of the victim, remaining as exoerythrocytic forms before entering the red blood cells to become trophozoites, periodically the red blood cells are ruptured and uninucleate individuals, called merozoites, are liberated into the plasma where they attack further red blood cells to become trophozoites again. This period in the dev elopment repeats itself and coincides with the attacks of rigor and fever so well-known in malaria cases. Some of the re-formed trophozoites differentiate and become male and female gaetocytes which produce no further symptoms. These forms are however infective for the mosquitos and the sexual life is completed in the mosquito to produce sporozoites in its salivary glands. The existance of the exoerythrocytic forms, in man, of the parasite has been a question of some doubt and much controversy. The problem seems, however, to be much nearer solution as a result of the work of Shortt, Garnham, Covell and Shute (B.M.J., 1948, 547) who claim to have found the pre-erythrocytic forms of P. vivax in the liver of a patient some seven days after infection.

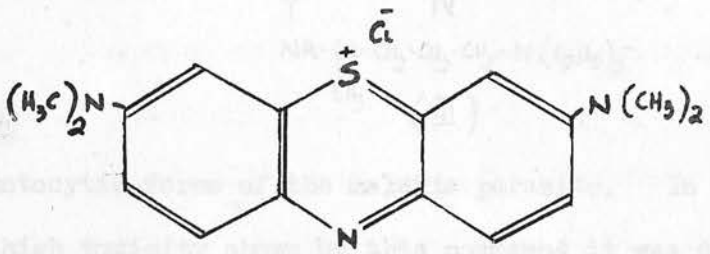
It has been suggested that these exoerythrocytic forms of the parasite are the cause of the relapses which occur in malaria and would be presumably the forms in the blood of "recovered" patients.

From consideration of the life cycle just mentioned, it can be seen that if the mosquito-half of the development were interrupted then this would provide an effective means of preventing the disease. This has been achieved by attacks on the mosquito larvae in the breeding grounds with insecticides and larvicides. The cheapest and most effective agent for this work is the new insecticide D.D.T. which is more toxic to the larvae and is effective for a much longer time than any substance used hitherto.

A further method of achieving this interruption in the life cycle of the parasite is to prevent the entry of the sporozoites from the bite of the mosquito. Some success in this direction has been achieved by the use of the new insect repellents, principally dimethyl phthalate. The attack, however, on the phase of the life-cycle of the malaria parasite within its human victim has been the particular aim of the chemotherapeutic approach to the disease.

This method had its beginnings in the sixteenth century with the use of cinchona bark. Pure quinine was isolated from this bark in 1820 by Pelletier and Caventou but little

advance was made until the elucidation of the structure of quinine by Rabe in 1908 allowed the chemical synthesis of similarly shaped compounds to be attempted. This represented the beginning of a synthetic method which has been used extensively in chemotherapeutic studies. From an observation by Ehrlich in 1891 that methylene blue (I) showed some antimalarial activity, Schülemann,

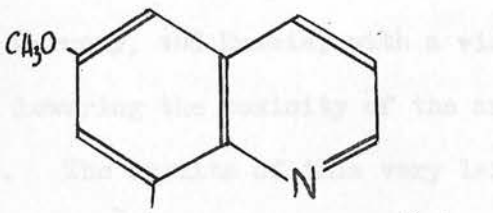


(I)

Schönhöfer and Wingler, (Proc. Roy. Soc. Med., 1932, 25, 897) of the I. G. Farbenindustrie, modified this molecule by substituting a diethylaminoethylamino group for one of the N-methyl groups and obtained a compound which when tested by Roehl in canaries infected with Plasmodium relictum was found to possess greater activity.

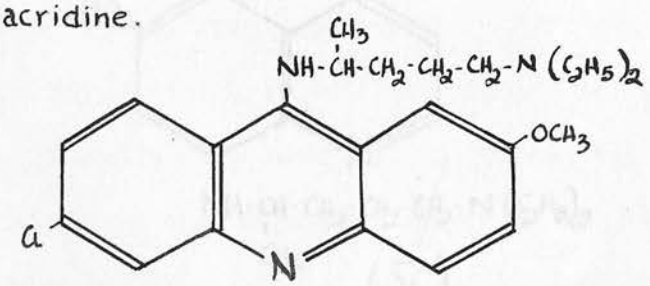
A decision to examine the quinoline nucleus led by the substitution of a diethylaminoalkylamino-grouping in the 8-

position of 6-methoxy-quinoline led to the discovery of plasmoquine (III) now known as pamaquin, which proved to be highly active against



(III)

the gametocytic forms of the malaria parasite. In view of a rather high toxicity shown by this compound it was decided to examine the substitution of these groups in other related heterocyclic ring systems, and Mietzsch and Mauss (Klin. Woch., 12, 1276-1278 (1933)) synthesised atebrine, now known as mepacrine (IV), 8-chloro-3-methoxy-5-(4-diethylamino-1-methylbutylamino)-acridine.

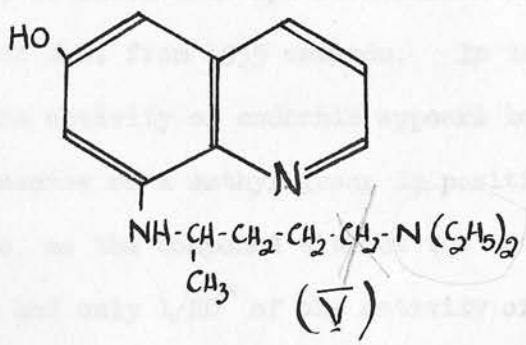


(IV)

which was tested by Kikuth and found to be a schizonticidal drug of considerably lower toxicity than pamaquin.

These two drugs, pamaquin and mepacrine, acted as models for most of the antimalarial research which was carried out until practically the outbreak of the World War II. Exhaustive examinations were made of the quinoline and acridine nuclei in Britain, France, Germany, and Russia, with a view to raising the activity and lowering the toxicity of the antimalarial agents available. The results of this very large volume of research did much to underline the value of mepacrine and the uniqueness of pamaquin.

Several compounds however have been described which have antimalarial activity of the same order as either mepacrine or pamaquin. Of these the most promising compound with gametocidal activity was certainly certuna (v), made by I.G. Farbenindustrie

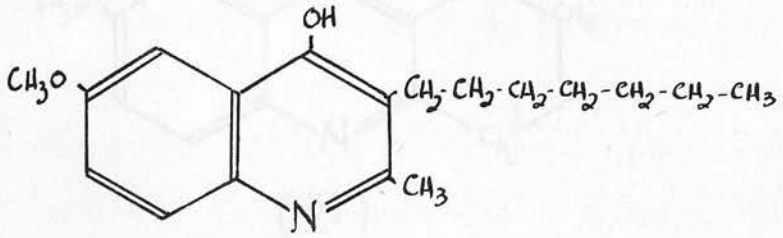


(V)

which is claimed to be less toxic and have an activity of the

same order as pamaquin. As demethylation has been suggested as a step in the metabolism of antimalarial drugs it is of interest to note that certuna has a hydroxyl group in position 6 of the nucleus in place of the methoxy group of pamaquin.

A compound, also made by I. G. Farbenindustrie in 1940, which has been reported as a causal prophylactic in avian malaria is shown in (VI). This drug, known as endochin, is

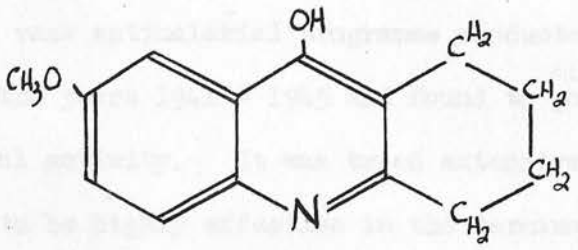


(VI)

the most active of the compounds of the 2:3-dialkyl-4-hydroxy-quinoline series, of which some 130 derivatives were studied by the chemists of I.G. from 1939 onwards. In this work it was found that the activity of endochin appears to depend in part upon the presence of a methyl group in position 2 of the quinoline nucleus, as the compound without the methyl group in this position had only 1/20th of the activity of the parent drug.

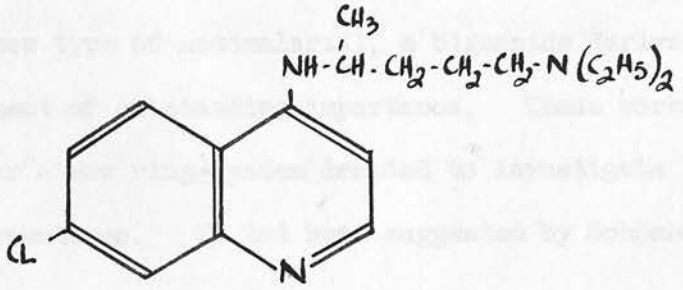
If the side-chain in position 3 of endochin is imagined

to be twisted into the form of a ring it may be regarded as related to the acridine nucleus and hence to mepacrine. In pursuance of this idea, Stephen, Tonkin, and Walker (J.C.S. 1947, 1034) synthesised some tetrahydro-acridones and found that 7-methoxy-1:2:3:4-tetrahydro-acridone (VII) was four times as active, on a weight basis, as endochin.



(VII)

Another series which received study from the chemists of I. G. Farbenindustrie from 1929 till 1943 during which time some 170 derivatives were prepared, consisted of compounds derived from 4-amino-quinoline. The most important compound of this series is resochin (VIII) 7-chloro-4-(4-diethylamino-1-methyl-butylamino)-quinoline



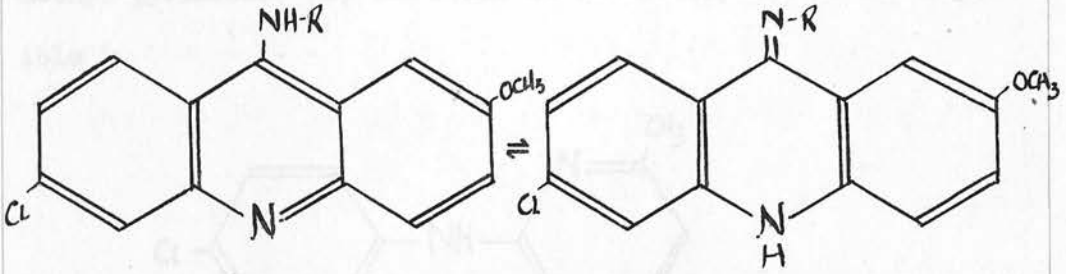
(VIII)

synthesised by Andersag and co-workers in 1935. This drug, however, was reported as being too toxic for practical use by Sioli and was abandoned in favour of the 3-methyl-derivative (sontochin), which was found to be as active as mepacrine in blood-induced B.T. malaria with no evidence of toxicity at three times the dose used for the clinical cures.

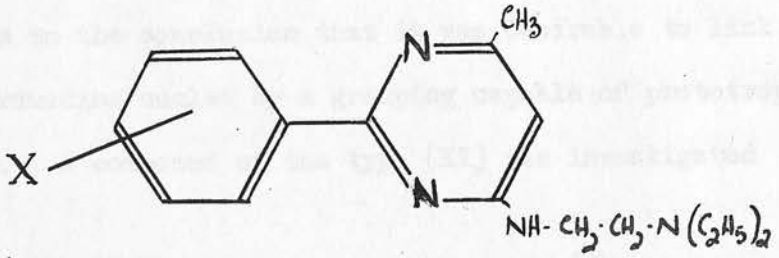
Resochin, known as chloroquine or SN 7618, was re-examined during the vast antimalarial programme conducted in the United States in the years 1941 - 1945 and found to possess marked antimalarial activity. It was tried extensively in humans and found to be highly effective in the termination of acute attacks of vivax malaria, the suppression of relapses, which was accomplished with doses of 0.3 g. at weekly intervals, and in treating blood-induced falciparum malaria. Chloroquine has, however, no prophylactic or relapse-preventing power in vivax malaria.

Despite the fact that over 12,500 drugs were tested by the Americans no real break-away from the standard structure for antimalarials has been achieved. Therefore the discovery by Curd, Davey, and Rose, of I.C.I. Ltd., in this country of a completely new type of antimalarial, a biguanide derivative, was a development of outstanding importance. These workers in a search for a new ring-system decided to investigate pyrimidine derivatives. It had been suggested by Schönhöfer

(Z. Physiol. Chem., 1942, 274,1) that the antimalarial action of mepacrine is connected with the possibility of tautomerism of the type:-



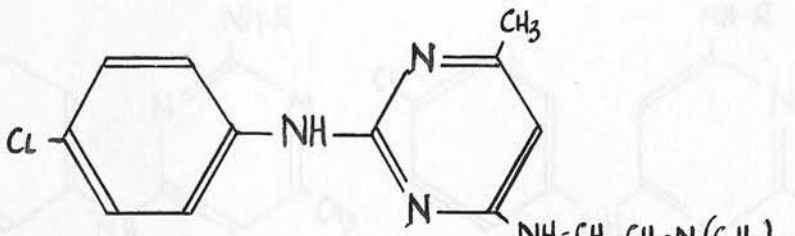
With this in view and in consideration of the substituents groups in the mepacrine structure, Curd, Rose, and Davey decided to investigate compounds of the type (IX)



X = p-Cl or m- or p-OCH3 (IX)

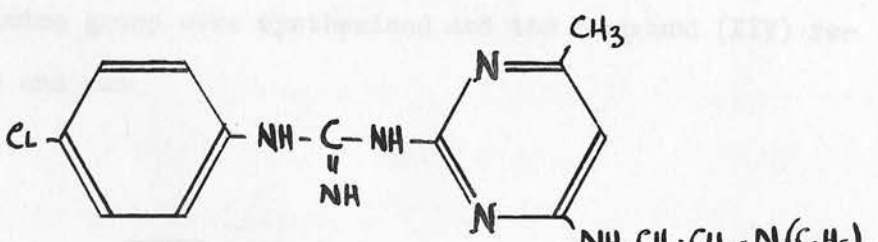
which would have a molecular weight of the same order as the well-known antimalarials, namely, between 300 and 400.

These compounds were found to be inactive against P. gallinaceum in chicks and so attention was turned to anilinopyrimidines and the compound 2-p-chloroanilino-3-(2-diethylaminoethylamino)-6-methyl-pyrimidine (x) was found to be active, but it was impossible



(X)

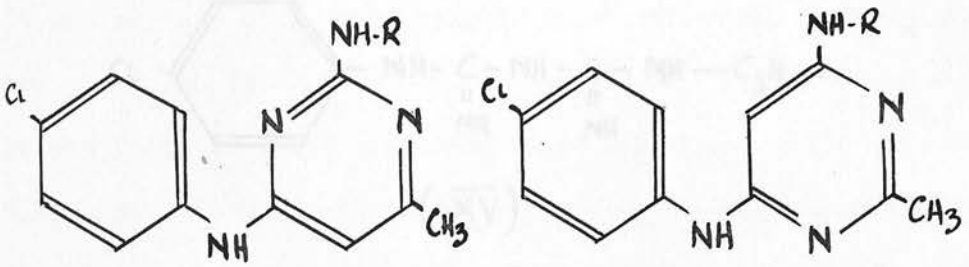
to carry out a clinical trial of this compound on man because of toxic effects. Comparison of types (IX) and (X) led these workers to the conclusion that it was desirable to link the aryl and pyrimidine nuclei by a grouping capable of prototrophic change. A compound of the type (XI) was investigated



(XI)

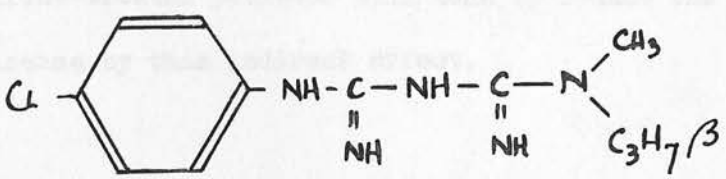
and in clinical tests it was found to be active against

P. vivax and P. falciparum but gave rise to toxic side effects. It had been found that certain isomers of the type (XII) of (X) had shown activity whereas isomers of the type (XIII) were devoid of all activity.



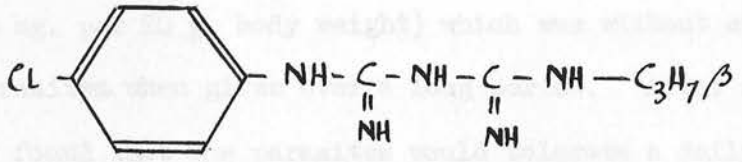
(XII) R = $-CH_2 \cdot CH_2 \cdot N(C_2H_5)_2$ (XIII)

And on study of these structures it seemed that activity was associated with the presence of two linked but independent amidine systems. Thus it was considered that perhaps two of the pyrimidine ring carbon atoms, 5 and 6, could be removed, and the resulting system was seen to be of the biguanide type. Further biguanide derivatives without the basic dialkylamino-alkylamino group were synthesised and the compound (XIV) resulted and was



(XIV)

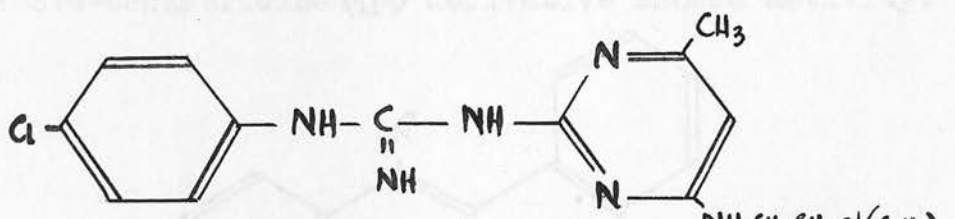
found to be active in human malaria. A further modification yielded an even more active compound (XV) which has been given the name paludrine (M.4888).



(XV)

In filed experiments Hamilton-Fairley (Trans. Roy. Soc. Med. Hyg., 40, 105 (1946)) found paludrine to be a good suppresive and a complete causal prophylactic in malignant tertian, producing a cure of this type of malaria more readily than mepacrine, and in vivax malaria to be a partial prophylactic. Further, insects which have ingested the blood of a paludrine-treated human being appears to absorb sufficient drug to prevent the development in the gut of the insect of the sexual forms of the Plasmodium. This means that such insects no longer function as vectors of malaria and so the mere presence of a number of paludrine-treated patients will tend to reduce the spread of the disease by this indirect effect.

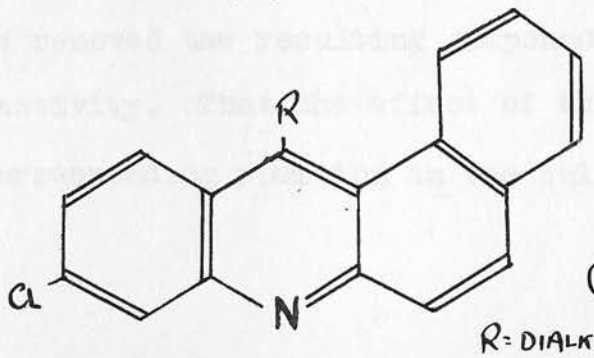
Acquired resistance to paludrine in P. gallinaceum in chicks has been reported by Bishop and Birkett (Nat., 159, 884 (1947)). These workers treated a normal strain of P. gallinaceum, paassaged intravenously through chicks every second or third day, with the largest dose of paludrine hydrochloride (0.025 mg. per 20 g. body weight) which was without effect upon the parasites when given over a long period. After a month it was found that the parasites would tolerate a daily dose of 0.05 mgs., after $4\frac{1}{2}$ months the parasites, normal in appearance, were receiving two doses daily of 1mgm. each, which is the largest dose that the host will tolerate. It is of interest that these paludrine-resistant strains were also resistant to the methyl-homologne of paludrine but not resistant to mepacrine. Sterilization of the gut of the mosquito, as mentioned above, no longer occured, and ~~that~~ the resistance persisted after three and five passages through the mosquito without intervening drug treatment. These results were confirmed by a paper published simultaneously by Bertram. Lourie, and Williamson (Nat., 159, 885, (1947)) in which they reported that they were unable to produce resistance in P. gallinaceum to quinine, mepacrine, sulphadiazine, and the pyrimidine derivative of type (XVI),



(XVI)

after 27-29 months of intensive treatment of serially infected chicks. With paludrine a high degree of resistance appeared within three months. This paludrine-resistant strain was found also to be resistant to N-5-methyl-paludrine. It would seem that active pyrimidine compounds can act upon strains of P. gallinaceum which have become insensitive to paludrine and methyl-paludrine; a result which suggests that the biochemical mechanism interfered with by paludrine is not the same as that interfered with by drugs of the pyrimidine series.

As mentioned earlier, the structures of the drugs pamaquin and mepacrine have acted as models for much antimalarial research. For example, the effect of adding on a benzene or pyridine ring to structures of the mepacrine-type has been investigated by Dobson and Kermack (J.C.S., 1946, 156), Hutchison and Kermack (ibid., 1947, 678), and Dobson, Hutchison, and Kermack (ibid., 1946, 623). These authors report that 8-chloro-5-(diethylaminopropylamino)-1:2-benzacridine (cf. Bachman and Picha, J.A.C.S., 1946, 68, 1599) is inactive against P. gallinaceum in chicks but that the 3:4-benzacridine (XVII) derivative showed activity.



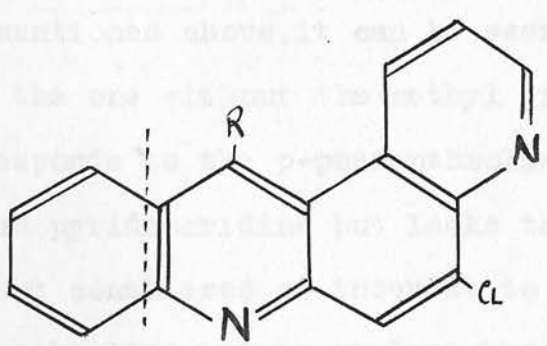
(XVII)

R = DIALKYLAMINOALKYLAMINO.

In an examination of the pyrido-acridines, the 8-chloro-1:2:2':3'-, -1:2:3':2'-, and 3:4:3':2'-pyrido-acridines with side-chains in position 5 were synthesised. It was found that the 3:4:2'3'-pyrido-acridine was active and further examination of this series was made. The effect of variation in the side-chain in position 5 was studied and although changes in activity were not marked, the 3-butylamino-propylamino and the 4-diethylamino-1-methylbutylamino groupings appeared to be the most potent in P. gallinaceum infections in chicks. When the chloro-atom in position 8 of 5-diethylamino-alkylamino-3:4:2':3'-pyrido-acridine is removed the resulting compound is only slightly active. Comparison of compounds with the chloro-group in positions 2 and 8 showed that rather more activity appeared when the group was present in position 2. The effect of chloro-groups in both the 2 and 8 positions appeared to be favourable for activity, since 2:8-dichloro-(3-diethylaminopropylamino)-3:4:2':3':-pyridoacridine was the most active compound obtained by these workers, being as active, on a weight basis, as mepacrine. When the chloro-atom in the chloroquine or mepacrine series is removed the resulting compound has a much reduced activity. That the effect of the chloro-atom in the corresponding position in the chloroquine,

mepacrine and active benz- and pyrido-acridines is so similar suggests a comparison in more general terms. From this comparison it could be said that the chloroquine nucleus is the parent compound from which these other series are derived. Thus by the fusion of a further benzene ring the acridine series would result and by the further addition of either a benzene or a pyridine ring in the suitable position the active benz- and pyrido-acridine series would be formed.

It was of considerable interest therefore to determine if possible the validity of this sugestion. It was considered that if the chloroquine system were left intact in one of the active pyrido-acridines and the rest of the structure removed that the activity would be expected to remain in the resulting compound. Thus in 2-chloro-5-dialkylaminoalkylamino-3:4:2':3'-pyrido-acridine (XVIII) if the outer benzene ring is removed, a 9-chloro-p-phen-anthroline derivative is obtained.



(XVIII) R=DIALKYLAMINOALKYLAMINO-

This compound can be regarded as a chloroquine derivative with a pyridine ring fused on in position 5:6 and bears the same relation to chloroquine as the 8-chloro-3:4:2':3'-pyrido-acridine base bears to those of the mepacrine type.

During the past few years some closely related p-phenanthroline derivatives have been synthesised. 9-(3-diethylaminopropylamino)-p-phenanthroline has been prepared by Jacomb and Kermack (J.C.S., 1946, 62) but was found to be inactive against P.relictum in canaries. This compound may be regarded as a pamaquin-like base modified by the fusion of an extra pyridine ring in the 6:7 position. The p-phenanthroline derivatives with the diethylamino-ethylamino and diethylaminopropylamino groupings in position 4, and with or without a methyl group in position 2, have been synthesised by Kermack and Weatherhead (J.C.S., 1940, 1164) but showed no activity against P.relictum in canaries. From the considerations mentioned above, it can be seen that of these compounds the one without the methyl group in position 2 corresponds to the p-phenanthroline residue from the modified pyridoacridine but lacks the chlorine atom. It was thus considered of interest to synthesise 4-chloro-p-phenanthroline and to replace the chlorine atom with the 4-diethylamino-1-methylbutylamino group-

ing to make available for testing the

4-(4-diethylamino-1-methylbutylamino)-p-phenanthroline. From the same considerations it was desirable to prepare 9-chloro-4-(3-diethylamino-propylamino)-p-phenanthroline and so 4:9-dichloro-p-phenanthroline was synthesised and converted to this derivative by treatment with the appropriate amine.

Perviously Kermack and Weatherhead (loc. cit) had prepared 2-diethylaminoalkylamino-4-methyl-p-phenanthroline but this had been found inactive against P. relictum in canaries. Compounds of this type but lacking the methyl group in position 4 have now been synthesised through 2-chloro-p-phenanthroline. Various methods of synthesising 2-chloro-p-phenanthroline have been investigated and these are discussed fully in Section IIA below which also includes the preparation of 2:7-dichloro-p-phenanthroline.

In connection with the synthesis of the various chloro-and dichloro-p-phenanthrolines just mentioned an attempt was made to prepare the hitherto unknown 4:5-dichloro-p-phenanthroline. This work is included in Section IIB.

In the present thesis there is included a note

on some benzthiazole derivatives, which were prepared for testing against filarial infection in cotton rats. This forms Section V and describes a method suitable for the rapid preparation of 2-methyl-benzthiazole on a moderately large scale based on the work of Kiprianov, Smitnik, and Grigor'eva, (J. Gen. Chem. (U.S.S.R.) 6, 232-235 (1936)). The general methods used for the preparation of various styryl derivatives from 2-methyl-benzthiazole are also described, with specific examples to indicate experimental details.

II. GENERAL DISCUSSION.

As indicated in the introduction to this thesis, it was desired to synthesise derivatives of p-phenanthroline with substituents in positions 2 and 4, and thus the preparation of 2- and 4-chloro-p-phenanthroline derivatives was investigated.

In the following general discussion the chemical studies and biological results are grouped as under:

A. 2-Chloro-p-Phenanthroline derivatives:

(1) Preparation of p-phenanthroline N-oxide and its treatment with phosphoryl chloride.
(2) Synthesis of 2-chloro-p-phenanthroline.
(3) Preparation of p-phenanthroline di-N-oxide and its treatment with phosphoryl chloride.
(4) Synthesis of 2:7-dichloro-p-phenanthroline.

B. 4-Chloro-p-Phenanthroline derivatives.

(1) Synthesis of 4-Chloro-p-phenanthroline.
(2) Synthesis of 4:9-dichloro-p-phenanthroline.
(3) Synthesis of 4:5-dichloro-p-phenanthroline.

C. Preparation of Amines from Chloro-p-phenanthrolines.

D. Biological Results.

A(1) The Preparation of p-Phenanthroline N-oxide and its Treatment with Phosphoryl Chloride.

The aim in this section of the work is to prepare derivatives of p-phenanthroline with a chloro-group in position 2. This problem is essentially analogous to that of preparing 2-Chloro-quinoline derivatives and therefore mention is made in this account of some of the methods used and results obtained in the quinoline field.

The preparation of p-phenanthroline has been carried out by many investigators starting from either benzene or quinoline derivatives. The first synthesis was achieved by Skraup and Vortmann. (M., 4., 570, (1883)) from the tin double salt of p-phenylene diamine by treatment with glycerol, concentrated sulphuric acid, and nitrobenzene. This method, however, because of the violent nature of the reaction and the presence of concentrated sulphuric acid gives poor yields. A modified method was described in B.P. 394,416 (1932) in which the concentrated sulphuric acid was replaced by 69% acid with the consequent promotion of a much less violent reaction and much improved yields due to a lessening of the amount of tarring.

This modified Skraup reaction has been found convenient for the preparation of p-phenanthroline from p-phenylene diamine in good yields.

In general it is found that quinoline and related compounds from N-oxides fairly easily on treatment with organic peracids. The first acid to be used in this connection was perbenzoic acid, which Meisenheimer (Ber., 1926, 59, 1848) utilised to prepare the N-oxides of pyridine, quinoline, and isoquinoline. It was used similarly some years later for the preparation of the quinoline oxide by Bobranski. (Ber., 1936, 69, 1113; 1938, 71, 578).

The preparation of perbenzoic acid is however laborious and the introduction of perphthalic acid is said to simplify the method of preparation of these oxides. Perphthalic acid (Org. Syn. 20, 70 (1940))was used by Bachman & Cooper (J. Org. Chem. 9, 302 (1944)) to obtain the N-oxides of 6-methoxy-, 6-chloro-, 6-nitro-, and benzo-(f)-quinoline. An interesting paper by Gouley, Moersch, & Mosher (J.A.C.S., 69, 303, 1947)) described the preparation of 5-nitroquinoline-N-oxide using the perphthalice acid method, and, although 8-acetylamino-6-methoxy quinoline-N-oxide was obtained, 8-nitroquinoline did not yield the corresponding compound. A method used in the pyrazine field to prepare pyrazine N-oxide has been extended to 5-nitroquinoline by Bachman & Wetzel (Private Communication 1946), who prepared the corresponding oxide by treating 5-nitroquinoline with hydrogen peroxide in glacial acetic acid.

It has also been found by Renfrew (J.A.C.S.,

68, 1433 (1946)) that 7-methylquinoline will yield an N-oxide on treatment with hydrogen peroxide. This method is less expensive and laborious but the yield is usually much inferior to that obtained by the perphthalic method.

m-Phenanthroline N-oxide has been prepared by Kermack & Tebrich (J.C.S., 1945, 374) by treating m-phenanthroline with perbenzoic acid.

This method has now been applied to the p-phenanthroline series and the mono-N-oxide, m.p. 233-234°, was obtained in 30% of the theoretical yield, along with some unchanged p-phenanthroline and some impure di-N-oxide.

In the analogous reaction reported above with m-phenanthroline Kermack and Tebrich do not record the isolation of any of the di-N-oxide derivative. That this is probably due to the differing reactivities of the two nitrogen atoms seems likely from the work of Kermack and Webster (J.C.S., 1942, 213) who found that only one methosulphate of m-phenanthroline could be obtained and that in this compound the methyl group was attached to N1 as shown by its conversion to 2-chloro-m-phenanthroline. (See section A(2)).

The treatment of N-oxides with sulphuryl chloride was first investigated by Meisenheimer (Ber., 1926, 59, 1852) who refluxed quinoline N-oxide with sulphuryl chloride and obtained a good yield of 4-chloro-quinoline

and does not report the isolation of any isomeric compound. Bobranski (Ber., 1936, 69, 113) used this reaction for the preparation of 4-chloro-quinoline as an intermediate in the synthesis of Kynurin (4-hydroxy-3-aldehydro-quinoline) but reinvestigated the reaction, (Ber., 1938, 71, 578), and found that Meisenheimer, who had isolated his chlorinated product as a picrate from alcohol, had not obtained any 2-chloro-compound as its picrate was quite soluble in ethanol. Bobranski modified the treatment of the crude chlorinated product and separated from it 62% of 4-chloro - and 38% of 2-chloro-quinoline, a little tetrachloroquinoline was also obtained from residual liquors. Magidson & Rubzov (J. Gen. Chem. (U.S.S.R.), 7, 1896, (1937)) treated 6-methoxy-quinoline N-oxide with both sulphuryl chloride and phosphoryl chloride. The results with sulphuryl chloride were unusual in that they obtained three dichloro-derivatives and one trichloro - derivative, with phosphoryl chloride however they got the expected 2 - and 4 - chloro-6-methoxy-quinolines. A further study of the reaction was made by Bachman & Cooper (J. Org. Chem., 9, 302 (1944)) who came to the conclusion that the nature of any substituent present in the 6-position drastically modifies the ratio of 2- and 4-chloro-derivative obtained and, further, that changes in reaction conditions appear to have very little influence on the ratio, for example, carbon tetrachloride was used as solvent in

in the treatment of 6-methoxy-quinoline N-oxide with phosphoryl chloride without appreciable effect on the reaction. The oxide, oxide dihydrate or oxide hydrochloride can be used although catalysts like sulphuric acid, acetic acid, or phosphorus pentoxide cause undesirable side-reactions. The following table shows some of the results obtained, quinoline has been added for comparison.

Material chlorinated.	Ratio of Isomers Obtd. 2:	4:	3:
Quinoline N-oxide.	1	1.7	
6-methoxy- " "	1	0.6	
6-Chloro- " "	1	1.38	
6-Nitro- " "	1	3.53	0.22

That Bachman and Cooper isolated some 3-chloro-isomer on treatment of 6-nitroquinoline N-oxide is interesting, and it parallels the results of Gouley, Moersch and Mosher (J.A.C.S., 69, 303 (1947)) with 5-nitroquinoline N-oxide, which on treatment with phosphoryl chloride gave 2-chloro-5-nitro-, 4-chloro-5-nitro-, and 3-chloro-5-nitroquinoline in the ratio 1:0.28:0.56. It is interesting to compare the ratios of isomers obtained with the 5-nitro- and 6-nitro-quinolines, when it can be seen that the 2-chloro-isomer was 54% of the yield in the 5-nitro experiment and only 21% in the 6-nitro-quinoline

experiment. The 4-chloro-isomer was 15% and 74% in the two series, while the 3-chloro was 30% and 5% respectively.

Sometimes the presence of certain substituents may seriously disturb the course of the reaction, e.g. with 8-nitro-quinoline the method fails because 8-nitro-quinoline does not form an N-oxide, whilst Gouley, et al. report that 6-methoxy-8-acetylamino-quinoline forms an N-oxide which however on treatment with phosphoryl chloride yielded a purple infusible solid which resisted all attempts at purification. On the other hand the reaction may proceed quite normally with the substituent, even a fairly bulky one in the 2-position, thus 2-p-chloro-phenyl-6-methoxy-quinoline N-oxide (Gilman and Spatz, J.A.C.S., 66, 62 (1944)) on treatment with phosphoryl chloride yields the 4-chloro-derivative.

This type of reaction has been carried out in the m-phenanthroline series by Kermack and Tebrich (J.C.S., 1945, 375) who obtained the 2-chloro-m-phenanthroline only from treatment of the N-oxide with phosphoryl chloride. These workers, also, used sulphuryl chloride but obtained a dichloro-derivative whose structure was determined.

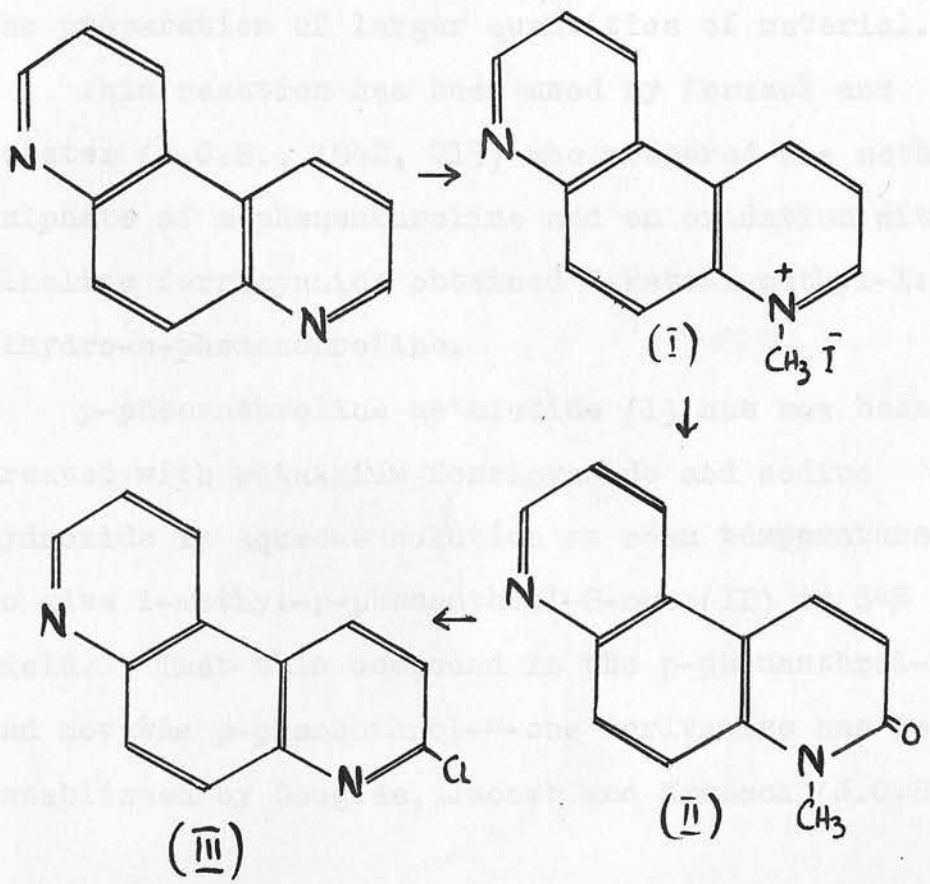
It is now found in the p-phenanthroline series

that when the mono-N-oxide, m.p. 233-234°, was treated with phosphoryl chloride under reflux the main product isolated, m.p. 190-191°, was undoubtedly the 2-chloro-isomer as shown by its identity with a specimen of 2-chloro-p-phenanthroline, m.p. 190-191°, prepared by an independent route discussed in detail in Section A (2). A small amount of by-product, m.p. 110-120°, which may correspond to the 4-chloro-isomer, was isolated but due to lack of material further purification was not achieved.

(2) Synthesis of 2-chloro-p-phenanthroline.

To ascertain the position of the chloro-group in the product obtained from the treatment of p-phenanthroline-N-oxide with phosphoryl chloride it was necessary to obtain 2-chloro-p-phenanthroline by a completely independent method.

The following series of reactions, involving the oxidation of the monomethiodide of p-phenanthroline (I) and the treatment of the resulting 1-methyl-p-phenanthrol-2-one (II) with phosphorus pentachloride and phosphoryl chloride, to yield the desired 2-chloro-p-phenanthroline (III) was investigated.



The preparation of the required methiodide (I) was achieved smoothly in 80% yield by refluxing p-phenanthroline in nitrobenzene with methyl iodide.

The oxidation of methiodides to the N-methyl-2-keto-compounds was first carried out by Decker (J. pr. Chem. 45, 161 (1892)) who treated pyridine and quinoline methiodides with alkaline potassium ferricyanide and obtained the N-methyl-2-pyridone and-2-quinolone in good yields. This reaction was used for the preparation of the N-alkyl-pyridone by Fargher and Furness (J.C.S., 1915, 107, 690) who modified the procedure and made it convenient for the preparation of larger quantities of material.

This reaction has been used by Kermack and Webster (J.C.S., 1942, 213) who prepared the metho-sulphate of m-phenanthroline and on oxidation with alkaline ferricyanide obtained 2-keto-1-methyl-1:2-dihydro-m-phenanthroline.

p-phenanthroline methiodide (I) has now been treated with potassium ferricyanide and sodium hydroxide in aqueous solution at room temperature to give 1-methyl-p-phenanthrol-2-one (II) in 84% yield. That this compound is the p-phenanthrol-2-one and not the p-phenanthrol-4-one derivative has been established by Douglas, Jacomb and Kermack (J.C.S.,

1947, 1659) by its identity with the product of a Skraup reaction on 6-amino-1-methyl-carbostyril.

The treatment of N-alkyl-2-ketones with phosphorus pentachloride and phosphoryl chloride has been investigated by Fischer (Ber., 1898, 31, 609) who obtained 2-chloro-pyridine and 2-chloro-quinoline by refluxing the corresponding 1-methyl-pyridone and 1-methyl-quinolone compounds with phosphorus pentachloride and phosphoryl chloride. Some years later the yield in the pyridine series was improved by Fargher and Furness (J.C.S., 1915, 107, 690) by using less pentachloride and more phosphoryl chloride than Fischer.

The application of this reaction in the m-phenanthroline series was shown by Kermack and Webster (~~ibid.~~ loc. cit.), who treated 2-keto-1-methyl-1:2-dihydro-m-phenanthroline with phosphoryl chloride and phosphorus pentachloride under reflux and obtained 2-chloro-m-phenanthroline.

2-chloro-p-phenanthroline (III), m.p. 190-191°, has now been prepared by the reaction of 1-methyl-p-phenanthrol-2-one (II) with phosphoryl chloride and phosphorus pentachloride in a sealed tube at 150° for five hours.

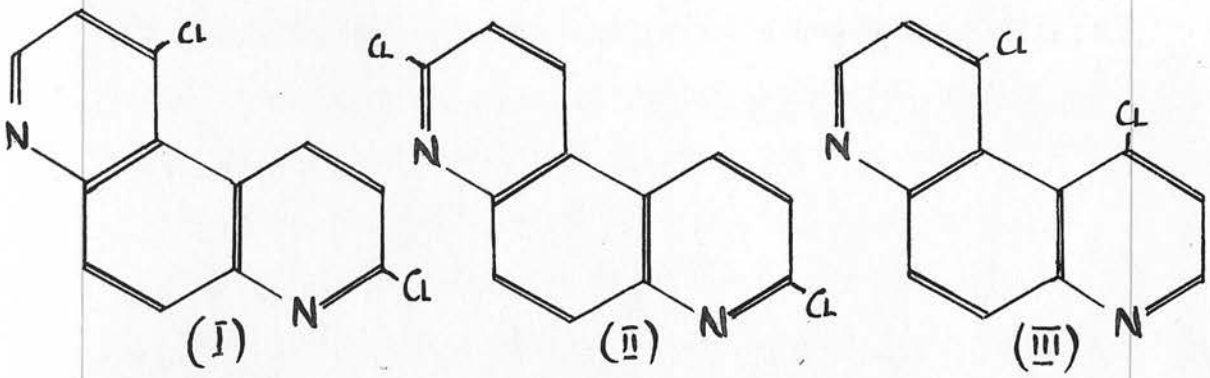
The product thus obtained was used for comparison with the compound obtained from the treatment of p-phenanthroline-N-oxide with phosphoryl chloride and proved by mixed melting-point determinations to be identical.

(3) Preparation of p-phenanthroline di-N-oxide and its Treatment with Phosphoryl Chloride.

As a by-product in the preparation of the mono-N-oxide of p-phenanthroline some impure di-N-oxide was isolated, and it was found that by using a larger proportion of perbenzoic acid, the di-N-oxide could be obtained in 75% yield. In this connection, it has already been mentioned that on treating m-phenanthroline with perbenzoic acid only the mono-N-oxide was obtained by Kermack and Tebrich (J.C.S., 1945, 375). In apaper published while this work was in progress Linsker and Evans (J.A.C.S., 68, 403, (1946)) describe the preparation of the di-N-oxides of o-, m-, and p-phenanthrolines by boiling the parent compounds with hydrogen peroxide in glacial acetic acid. The yield obtained of the p-phenanthroline di-N-oxide was 68% and the melting point was given as 308°. The melting point of the material obtained by the perbenzoic acid method was 325°. Linsker and Evans describe their compound as separating from hot water in yellow needles, whereas when our compound was recrystallised colourless needles were obtained. Like Linsker and Evans' compound our product was insoluble in most organic solvents and in cold water. It is worthy of note that Linsker and Evans found

that oxidising agents like chromic acid, selenium dioxide, vanadium pentoxide, iodic acid and periodic acid had no effect on m- and p-phenanthrolines.

When the quinoline N-oxide is treated with phosphoryl chloride 2- or 4-chloroquinoline is obtained. It follows then from the treatment of p-phenanthroline di-N-oxide with phosphoryl chloride we might expect that three dichloro-derivatives might be formed,



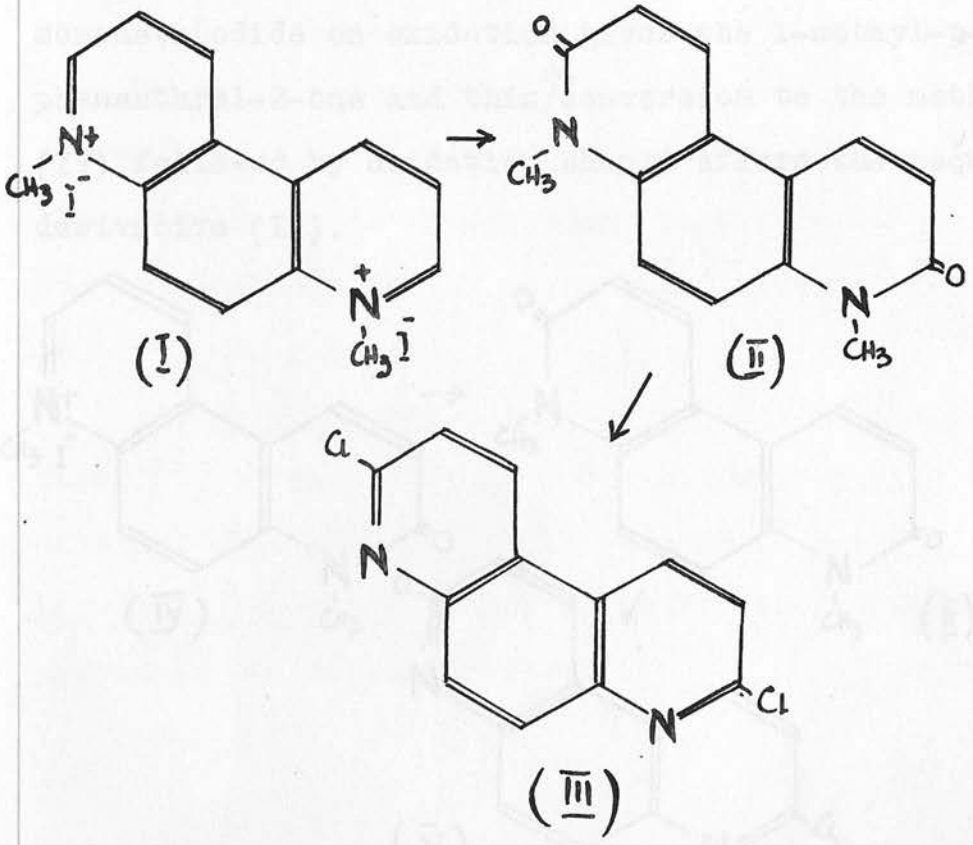
2;5-dichloro- (I), 2:7-dichloro- (II), and 4;5-dichloro-p-phenanthroline (III). However, from the fact that when phosphoryl chloride reacts with the mono-N-oxide the 2-chloro-compound is obtained it seemed that the 2:7-dichloro-derivative was the most probable.

p-phenanthroline di-N-oxide, m.p. 324-325°, was refluxed with phosphoryl chloride for five hours at 125° and gave, in fact, a single dichloro-compound, m.p. 315-316°.

An authentic specimen of 2:7-dichloro-p-phenanthroline, (II), m.p. 315-316°, was therefore prepared by an unambiguous method to be described in Section A (4). This compound was found to be identical with the compound, m.p. 315-316°, just referred to. We therefore conclude that when phosphoryl chloride acts on p-phenanthroline di-N-oxide the product is 2:7-dichloro-p-phenanthroline.

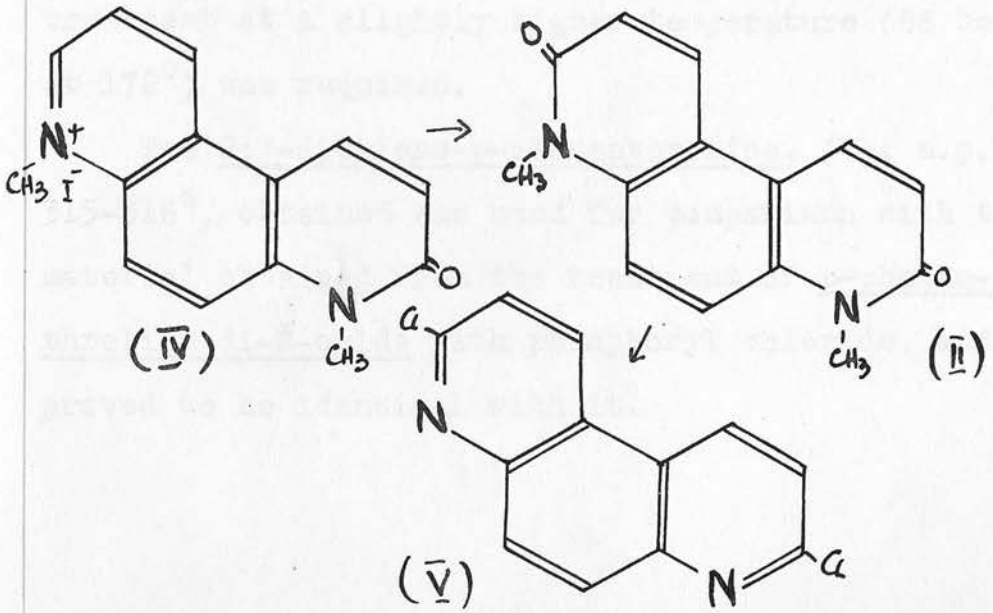
(4) Synthesis of 2:7-dichloro-p-phenanthroline.

The experience gained in the synthesis of 2-chloro-p-phenanthroline described in Section A (2), suggested a method for the preparation of 2:7-dichloro-p-phenanthroline. It seemed therefore that the dimethiodied of p-phenanthroline (I) on alkaline oxidation with potassium ferricyanide would yield the 2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-p-phenanthroline (II), and that treatment of this compound with phosphoryl chloride and phosphorus pentachloride would lead to the required 2:7-dichloro-p-phenanthroline. (III)



Attempts were made to prepare the required dimethiodide without success. p-phenanthroline was refluxed with excess of methyl iodide in nitrobenzene in differing proportions and for varying periods of time, but in all the experiments conducted, the product obtained was the monomethiodide, m.p. 270-271°. This, too, was the sole product when p-phenanthroline was heated with a large excess of methyl iodide in nitrobenzene in a sealed tube.

It was therefore decided to attempt to prepare the diketo-dimethyl-p-phenanthroline derivative (II) by two successive applications of the reactions used in Section A (2), as we have seen p-phenanthroline monomethiodide on oxidation gives the 1-methyl-p-phenanthrol-2-one and this on conversion to the methiodide (IV) followed by oxidation should afford the required derivative (II).



It was found that the methiodide of 1-methyl-p-phenanthrol-2-one, m.p. 290-291°, could be formed smoothly and in good yield, 73% of theory, by refluxing 1-methyl-p-phenanthrol-2-one with methyl iodide in nitrobenzene and that the subsequent oxidation with alkaline potassium ferricyanide also proceeds easily and a good yield (89%) of the desired 2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-p-phenanthroline, m.p. 363-364°, was obtained.

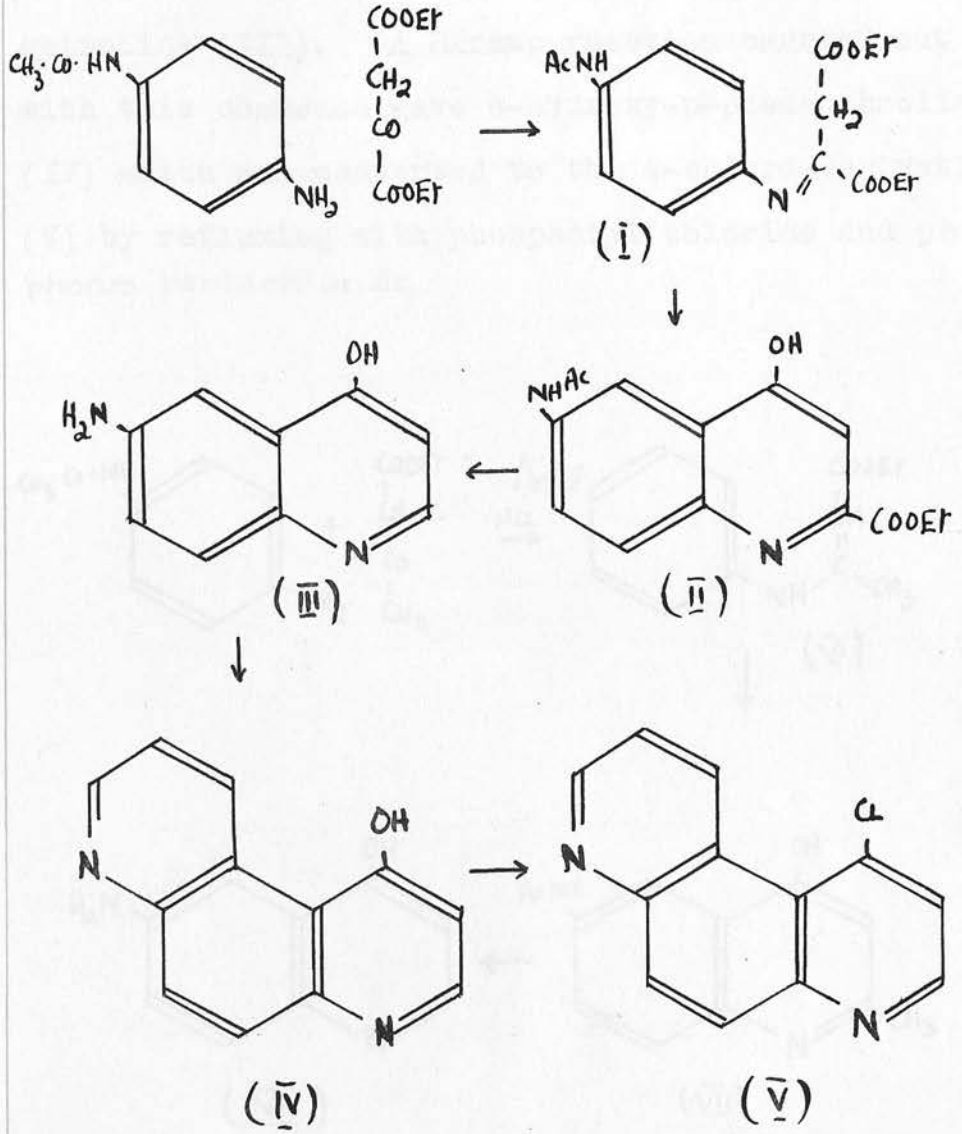
The diketo-dimethyl-compound was now heated with phosphorus pentachloride and phosphoryl chloride at 180° in a sealed tube in the expectation that like 1-methyl-2-keto-1:2-dihydro-p-phenanthroline it would react and be converted to the 2:7-dichloro-compound.

In small experiments of 1 g. this expectation was realised and a good yield was obtained, but in larger experiments it was found that much longer treatment at a slightly higher temperature (86 hours at 172°) was required.

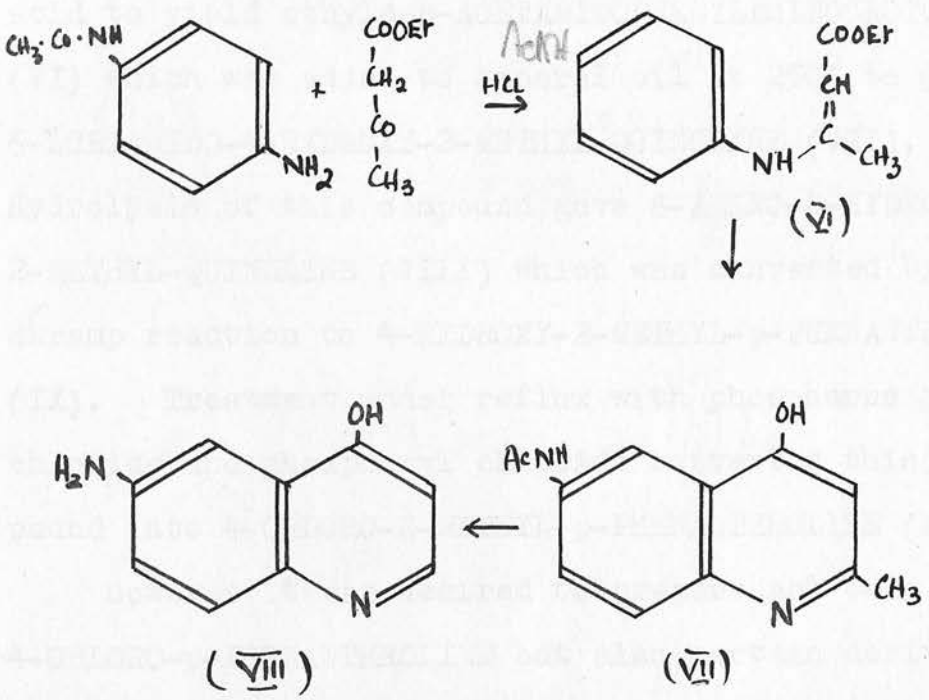
The 2:7-dichloro-p-phenanthroline, (V), m.p. 315-316°, obtained was used for comparison with the material obtained from the treatment of p-phenanthroline di-N-oxide with phosphoryl chloride, and proved to be identical with it.

B (1) SYNTHESIS of 4-CHLORO-p-PHENANTHROLINE.

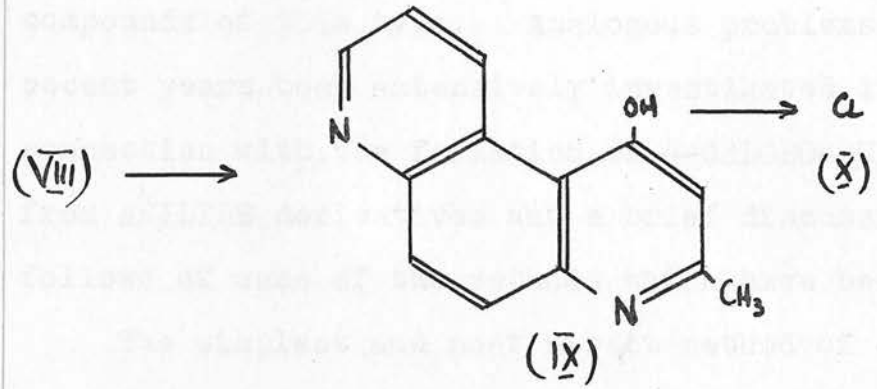
4-chloro-p-phenanthroline and its 2-methyl analogue have been prepared previously by Kermack and Weatherhead. These authors (J.C.S., 1940, 1167) synthesised the 4-chloro-derivative by the following method:-



p-AMINOACETANILIDE was condensed with ETHYL OXALOACETATE to give ETHYL α-p-ACETAMIDOANILINO-FUMARATE, (I), which was isolated and added to mineral oil at 250-260° to yield ethyl 6-acetamido-4-hydroxy-quinoline-2-carboxylate, which was saponified with acid and decarboxylated in quinoline with copper bronze as catalyst to give 6-amino-4-hydroxy-quinoline (III). A Skraup reaction carried out with this compound gave 4-hydroxy-p-phenanthroline (IV) which was converted to the 4-chloro-derivative (V) by refluxing with phosphoryl chloride and phosphorus pentachloride.



4-chloro-2-methyl-p-phenanthroline was synthesised (J.C.S., 1939, 563; 1940, 1167) starting from p-AMINOACETANILIDE and ethyl acetoacetate by the following steps:- (VI) - (X).

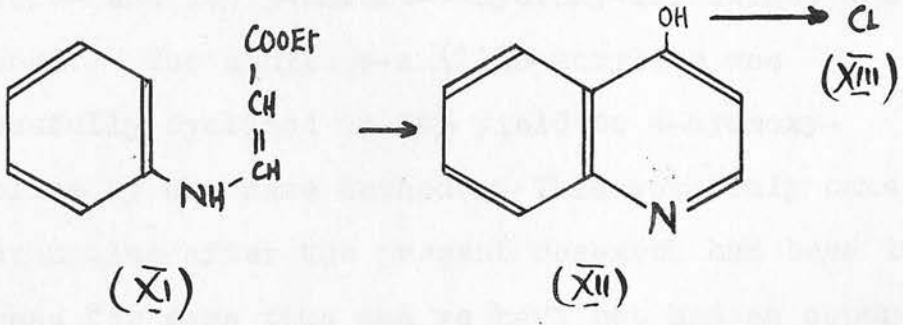


Ethyl acetoacetate was condensed with p-aminoacetanilide in presence of a trace of hydrochloric acid to yield ethyl β-p-ACETAMIDOPHENYLAMINOCROTONATE (VI) which was added to mineral oil at 250° to give 6-ACETAMIDO-4-HYDROXY-2-METHYL-QUINOLINE (VII). Hydrolysis of this compound gave 6-AMINO-4-HYDROXY-2-METHYL-QUINOLINE (VIII) which was converted by a Skraup reaction to 4-HYDROXY-2-METHYL-p-PHENANTHROLINE (IX). Treatment under reflux with phosphorus pentachloride and phosphoryl chloride converted this compound into 4-CHLORO-2-METHYL-p-PHENANTHROLINE (X).

However it was desired to prepare not only 4-CHLORO-p-PHENANTHROLINE but also certain derivatives such as 4:9-DICHLORO-p-PHENANTHROLINE for which

the methods were not suitable. As derivatives of 6-AMINO-QUINOLINE are readily available they form promising starting-out compounds for p-PHENANTHROLINE syntheses and so the problem arose as to the best method of fusing on a 4-CHLORO-PYRIDINE ring to compounds of this type. Analogous problems have in recent years been extensively investigated in connection with the formation of 4-CHLORO-QUINOLINES from ANILINE derivatives and a brief discussion follows of some of the methods which have been used.

The simplest and most direct method of obtaining 4-chloro-quinolines unsubstituted in position 2 would be by the cyclisation of a β-arylamino-acrylate followed by treatment with phosphoryl chloride, e.g. for the synthesis of 4-chloro-quinoline (XIII) it would be necessary to cyclise ethyl β-anilino-acrylate (XI), and to convert the resulting 4-hydroxy-quinoline (XII) to the 4-chloro-derivative (XIII).



(XI) (XII) (XIII)

However, this method had been reported as being unsuccessful due to the failure of the acrylates to cyclise, in particular, Rubtsov (J. GEN. CHEM., (U.S.S.R.), 7, 1885 (1937), C.A. 32, 526 (1938) asserts that ethyl β-p-anisidino-acrylate could not be cyclised to yield 6-methoxy-4-hydroxy-quinoline. Whilst the present work was in progress a paper was published by Price, Leonard and Reitsema (J.A.C.S., 68, 1256 (1946)).

These authors used aniline and m-chloroaniline and prepared the corresponding acrylates by the action of ethyl and methyl formylacetates (PECHMAN, BER., 25, 1040 (1892)), in the form of their sodio-derivatives, on the amines in acetic acid but the yield obtained was only 26%. An attempt to cyclise ethyl and methyl m-chloroanilino-acrylates in relatively concentrated diphenyl ether yielded bis-(m-chlorophenyl)-urea, but by using a much larger volume of diphenyl ether/diphenyl mixture the cyclised product, 40% 7-chloro- and 10% 5-chloro-4-hydroxy-quinoline, was obtained. The ethyl β-anilino-acrylate was successfully cyclised in 44% yield to 4-hydroxy-quinoline by the same method. This work only came to our notice after the present research had been in progress for some time and we have not had an oppor-

tunity of exploring the use of formylacetate with derivatives of 6-amino-quinoline.

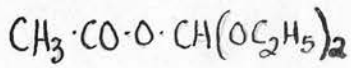
In the last few years a large amount of work has been done on this type of reaction with ethyl ethoxymethylene-malonate and by itsaid many derivatives of 4-hydroxy- and 4-chloro-quinoline have been prepared, especially in America in connection with the synthesis of antimalarial agents. Attention was turned to the use of ethyl ethoxymethylene-malonate with amines to form β-arylamino-α-carbethoxy-acrylates the cyclisation of which had been reported by Price and Roberts (J.A.C.S., 68, 1204 (1946)) to be of general application. Ethyl ethoxymethylene-malonate was first prepared by Claisen, (BER., 26, 2729 (1893); ANN., 297, 16, 77 (1897)) who obtained ethyl β-anilino-α-carbethoxy-acrylate from the reaction with aniline. The cyclisation of this acrylate was carried out by Gould and Jacobs (J.A.C.S., 61, 2890 (1929)) by heating in mineral oil at 250°, in the manner of Limpach (BER., 64, 969 (1931)), to yield 4-hydroxy-quinoline-3-carboxylate. These authors also showed that the reaction of ethyl ethoxymethylenemalonate with an amine could be extended to more complicated derivatives, e.g. by the condensation with methyl 3-amino-1-naphthoate

and cyclisation of the intermediate acrylate the benzo-(f)-quinoline derivative was obtained. Both the condensation of the ethoxymethylenemalonate with the amine and the subsequent cyclisation usually proceed smoothly and in good yield:

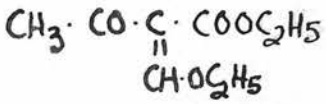
Riegel et al., (J.A.C.S., 68, 1264 (1946)) in a review of the routes to 4-halogeno-quinolines came to the conclusion that the route employing ethoxymethylenemalonate is very convenient and of very general applicability. It seemed to us to offer considerable promise for the preparation of the desired 4-chloro-p-phenanthrolines from 6-amino-quinoline derivatives and so was chosen for study in the present research.

The preparation of ethyl ethoxymethylenemalonate by the original method of Claisen has not always been successful in the hands of other investigators. With the object of improving the yield obtained in its synthesis, Fuson, Parham and Reed (J. ORG. CHEM., 11, 194 (1946)) studied the mechanism of the formation of ethyl ethoxymethylenemalonate. In the Claisen method, diethyl malonate, ethyl orthoformate, acetic anhydride and zinc chloride are heated together at 110-112° and the reaction was thought to be a simple condensation between diethyl malonate and

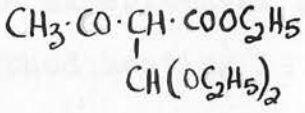
ethyl orthoformate, the ethanol being removed by the acetic anhydride. However Post and Erickson (J. ORG. CHEM., 2, 260 (1937)) had shown that ethyl ortho-formate reacts with acetic anhydride to form ~~ethyl~~ diethoxymethyl acetate (XIV) and acetic acid, and had, further, shown that ~~ethyl~~ diethoxymethyl acetate could react with ethyl acetoacetate to form ethyl α-(ethoxymethylene)-acetoacetate (XV) and acetic acid probably through the intermediate ethyl α-(diethoxy-methyl)-acetoacetate (XVI). Fuson et al. thus decided to investigate the possibility that diethyl malonate might be diethoxymethylated by diethoxymethyl acetate to produce diethyl diethoxymethylmalonate (XVII) which could lose ethanol to give diethyl ethoxymethylenemalonate (XVIII). These authors regard this possibility as confirmed by the isolation of diethyl diethoxymethylmalonate. This ester may, however, be formed by the interaction of ethyl ortho-formate and diethylmalonate. Whatever the mechanism is, the intermediate compound is formed in consider-able amount and it seemed likely that prolonged heating at a higher temperature without the removal of the zinc salts would improve the yield of ethoxy-methylenemalonate by decomposing the diethoxymethyl-malonate. These authors verified this expectation by experiment and obtained a 63% yield of ethyl



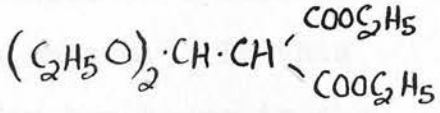
(XIV)



(XV)



(XVI)



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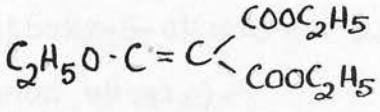

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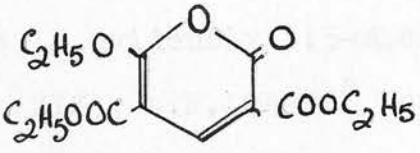


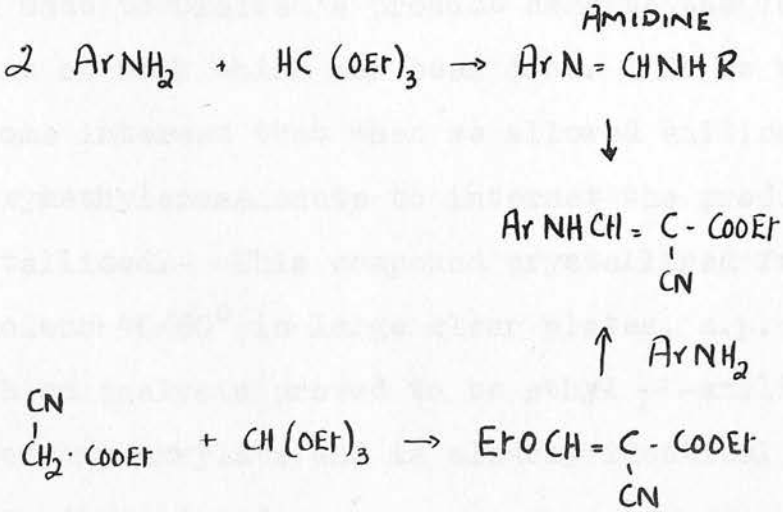
(XIX)

ethoxymethylenemalonate.

In the present research it has now been confirmed that ethyl ethoxymethylenemalonate may be prepared successfully by a similar method, the details of which were kindly supplied by Imperial Chemical Industries Ltd. and which is described in the Experimental part of this thesis. In this method heating is continued for ten hours in the presence of the zinc salts and a yield of 57% calculated on the amount of diethyl malonate used, was obtained. It may be added that in all the preparations carried out some non-volatile solid was obtained from the vacuum distillation of the reaction mixture, which crystallised from light petroleum 40/60°, M.P. 94-94°. This is evidently 3:5-dicarbethoxy-6-ethoxy-α-pyrone (XIX), M.P. 94-96° (cf. Fuson et al.).

It may be mentioned that Price, Leonard and Herbrandson (J.A.C.S., 68, 1264 (1946)) investigated the use of ethyl ethoxymethylenecyanacetate (de BOLLEMONT-BULL SOC. CHEM., (3), 25, 20 (1901)). However it was found that the preparation of this compound offered no advantage over the methylenemalonate synthesis and that the cyclisation of the acrylates formed with amines required much higher

volume of medium. Synder and Jones (J.A.C.S., 68, 1253, (1946)) simplified this method of preparation considerably by showing that it was possible to condense m-chloroaniline, ethyl orthoformate and ethyl cyanacetate directly by heating at 160°. without the separate preparation of the ethoxymethylene compound, and to obtain the acrylate derivative in excellent yield. These authors suggested the following two mechanisms for the reaction.



Before studying the reaction of ethoxymethylene-malonate with 6-amino-quinoline and its derivatives a preliminary condensation was carried out with aniline. Although Claisen reported that he had obtained a solid which crystallised from an ether/ligroin mixture in colourless plates, m.p. 50°, Schofield and Simpson (J.C.S., 1946, 1033) state that their compound was an oil which would not crystallise. In recent years no specific reference appears to have been made to Claisen's product despite the large amount of work which has been done. It is therefore of some interest that when we allowed aniline and ethoxymethylenemalonate to interact the product crystallised. This compound crystallised from light petroleum 40/60° in large clear plates, m.p. 46-47°, which on analysis proved to be ethyl β-anilino-α-carbethoxy-acrylate and is clearly identical with Claisen's compound.

The condensation of ethyl ethoxymethylene-malonate with 6-amino-quinoline was found to proceed smoothly when the two compounds were heated at 100°. The general procedure used was that of Schofield and Simpson (loc. cit.), the ethanol formed during the course of the reaction being removed by keeping the flask under reduced pressure. The product,

ETHYL β-6'-QUINOLYLAMINO- α-CARBETHOXY-ACRYLATE, (XX), which crystallised in large white rectangular plates, m.p. 97-98°, was obtained in good yield (95%). It is of interest to note that this compound dissolved readily in dilute hydrochloric acid but did not seem to be hydrolysed in the cold because on treatment with sodium nitrite solution and addition to alkaline β-naphthol solution, no colouration resulted.

The next step is to effect the cyclisation of the 6'-quinolyl-amino-acrylate (XIX) according to the following scheme.

Several methods have been used for the cyclisation of alkylidene derivatives. The original method suggested by Conrad and Limpach (BER., 20, 944 (1887)) was to heat the compound to about 240°. This method gave poor yields due to tarring and the formation of by-products; however, a much later paper by Limpach (BER., 64, 969 (1931)) described the use of mineral oil heated to 250° as cyclisation medium and recorded an imprpvement in yield from 30 to 90-95%. As mentioned earlier, Gould and Jacobs used this method successfully for the cyclisation of ethyl β-anilino-acrylate to give 4-hydroxy-quinoline. For this type of cyclisation, it has since been reported by Price

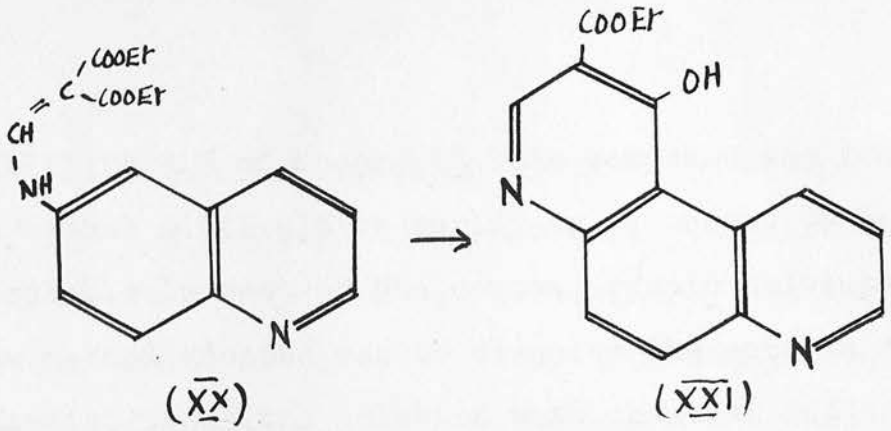
and Roberts (J.A.C.S., 68, 1204 (1946)) that diphenyl (m.p. 70°), diphenyl ether (m.p. 27°) and the eutectic mixture of these, Dowtherm A (m.p. 12°) are far superior as cyclisation media, their boiling points are at an optimum for cyclisation and they are much less viscous and more easily removed from the product by filtration, and, in general, the product is formed with much less darkening.

In a recent paper Stephen, Tonkin, and Walker (J.C.S., 1947, 1034) strongly recommend the use of diphenyl as solvent for carrying out cyclisations of this class.

In the present research the cyclisations have been carried out sometimes with mineral oil as solvent and sometimes with diphenyl.

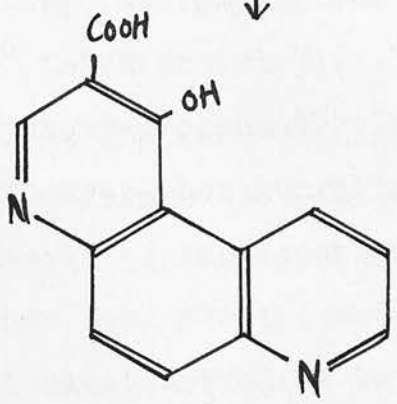
Ethyl β-6'-quinolylamino-α-carbethoxy-acrylate (XX) was added to mineral oil at 250-260° to give 4-hydroxy-3-carbethoxy-p-phenanthroline (XXI) in 91% yield. This product, crystallised from ethanol, melted at 285-286° and formed colourless rectangular prisms, which were soluble in dilute acid but not in alkali.

Hydrolysis of this ester was carried out by refluxing for six hours with 20% methanolic potassium hydroxide to yield 4-hydroxy-3-carboxy-p-phenanthroline

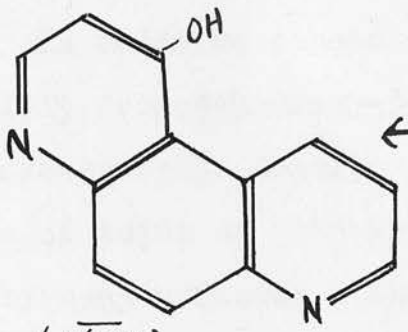


(XX)

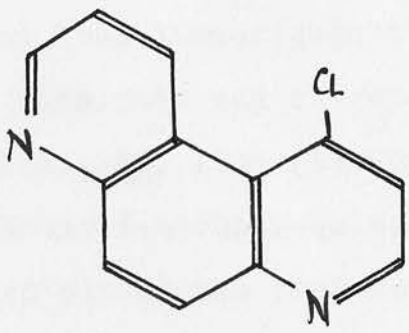
(XXI)



(XXII)



(XXIII)



(XXIV)

(XXII) in 91% of theory. This compound was found to be rather difficult to purify as it proved to be insoluble in most of the common organic solvents. The method adopted was to dissolve the acid in dilute ammonia, treat the solution with charcoal and to re-precipitate the solid with dilute acetic acid. Treatment by this method three times gave cream micro-needles, m.p. 307-308° (with frothing).

In order to obtain 4-hydroxy-p-phenanthroline (XXIII) from 4-hydroxy-3-carboxy-p-phenanthroline it is necessary to decarboxylate it. The decarboxylation of acids of this type has been studied extensively by many workers. The simplest method is to heat the dry acid to a temperature above its melting point when carbon dioxide is liberated. This method is satisfactory for small quantities of compound but is rather wasteful when larger quantities are used. The effect of catalysts was investigated by Price and Roberts (J.A.C.S., 68, 1204 (1946)) who found with 7-chloro-4-hydroxy-3-carboxy-quinoline that decarboxylations carried out in the presence of powdered glass or copper-chromite catalyst indicated no favourable effect on lowering the temperature or increasing the rate at which loss of carbon dioxide occurred. When considerable quantities of acid have to be decarboxy-

lated it is often most convenient to heat them in a solvent and the combination of the use of a solvent with the use of a catalyst often gives very satisfactory results. Thus Kermack and Weatherhead, as mentioned earlier, heated 6-acetamido-4-hydroxy-2-carboxy-quinoline in boiling quinoline in the presence of copper bronze as catalyst and obtained 6-acetamido-4-hydroxy-quinoline.

Decarboxylation of 4-hydroxy-3-carboxy-p-phenanthroline (XXII) was achieved by refluxing in dry quinoline with a little copper-barium-chromite catalyst (CONNOR, FOLKERS and ADKINS, J.A.C.S., 54, 1138 (1932)) for forty-five minutes. The catalyst was separated by filtration and the quinoline removed by steam distillation. The resulting aqueous solution was evaporated to dryness and the residue crystallised from water to give 4-hydroxy-p-phenanthroline, m.p. 300-301°, (XXIII) in almost quantitative yield. 4-hydroxy-3-carboxy-p-phenanthroline was also decarboxylated conveniently in small quantities by heating in a test-tube either in a metal-bath or a free flame above its melting point. The product obtained has the same melting point as the compound obtained by the other route. This hydroxy-compound was found to be identical in melting point

with a specimen prepared by Kermack and Weatherhead (loc. cit.) by the method outlined earlier; their melting point was given as 298°.

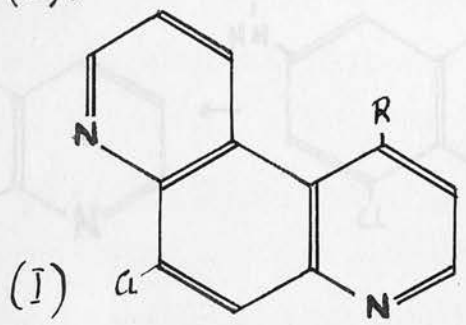
4-chloro-p-phenanthroline, m.p. 146-147°, (XXIV), was obtained smoothly from 4-hydroxy-p-phenanthroline by heating with phosphorus pentachloride and phosphoryl chloride, (cf. KERMACK and WEATHERHEAD, 1940, 1164). The compound prepared by Kermack and Weatherhead was stated to have a melting point of 147°.

It has been assumed that ethyl 6'-quinolylamino-α-carbethoxy-acrylate would cyclise to form the angular compound and not the linear compound. On general grounds there seems little doubt of the correctness of this expectation and the fact that the decarboxylation product is identical with that previously obtained by Kermack and Weatherhead is a strong confirmation, as there seems little doubt that their compound has the angular structure, being formed by the Skraup reaction on 4-hydroxy-6-amino-quinoline. Skraup reactions seem invariably when possible to lead to the angular and not the linear form.

In the other cyclisations with ethyl ethoxy-methylenemalonate described below it is assumed without further proof that the angular compounds are formed and not the isomeric linear diazanthracenes.

(2) SYNTHESIS OF 4:9-DICHLORO-p-PHENANTHROLINE.

As explained in the introduction to the thesis it was considered highly desirable to obtain compounds of type (I).

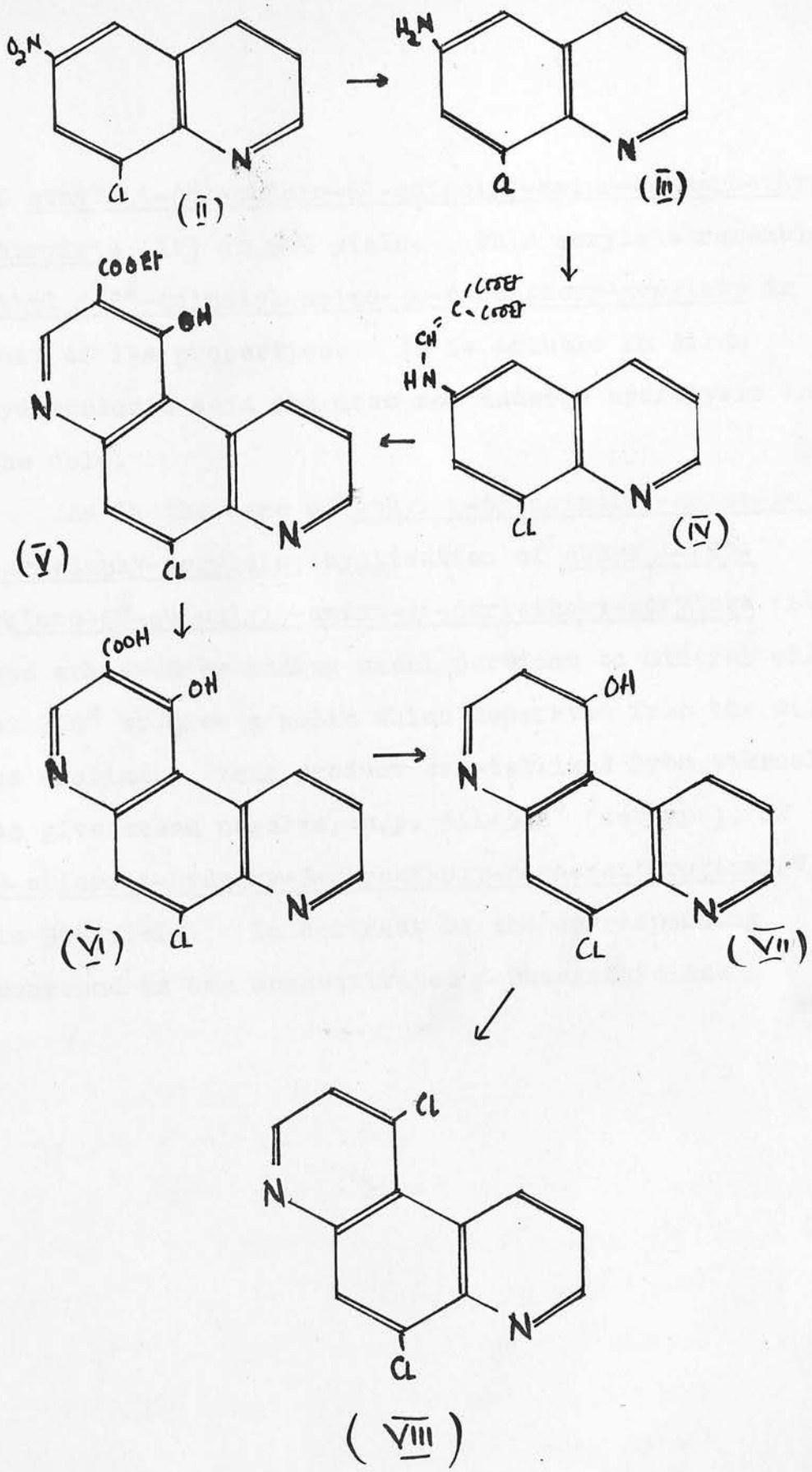


(I)

R = DIALKYLAMINO-ALKYLAMINO.

For this purpose it was necessary to attempt to prepare 4:9-dichloro-p-phenanthroline as this compound when treated with suitable aimines such as diethylaminopropylamine should yield bases of the desired type. 4:9-dichloro-p-phenanthroline should be obtained from 6-amino-8-chloro-quinoline by the following series of reactions.

6-nitro-8-chloro-quinoline (II) was obtained from 2-chloro-4-nitraniline by a modified Skraup reaction (cf. B.P. 394, 416) in 54% yield and reduction by West's method (J.C.S., 1925, 127, 494) gave 6-amino-8-chloro-quinoline (III) in 92% yield. The condensation of ethyl ethoxymethylenemalonate and 6-amino-8-chloro-quinoline was carried out at 100° and the solid product obtained crystallised from ethanol to give yellow-orange needles, m.p. 141-142°


O2N
Cl
N
(II)
H2N
Cl
N
(III)
COOEt
OH
N
N
Cl
(V)
CH
C(COOEt)2
HN
N
Cl
(IV)
COOH
OH
N
N
Cl
(VI)
OH
N
N
Cl
(VII)
Cl
N
N
Cl
(VIII)

of ethyl β-(8'-chloro-6'-quinolyl)-amino-α-carbethoxy-acrylate (IV) in 94% yield. This acrylate resembles ethyl β-6'-quinolyl-amino-α-carbethoxy-acrylate in most of its properties. It is soluble in dilute hydrochloric acid and does not undergo hydrolysis in the cold.

As in the case of ethyl β-6'-quinolyl-amino-α-carbethoxy-acrylate, cyclisation of ethyl β-(8'-chloro-6'-quinolyl)-amino-α-carbethocy-acrylate (IV) was achieved by adding small portions to mineral oil at 250° to give a solid which separated from the oil on cooling. This product crystallised from ethanol to give cream needles, m.p. 311-312° (decomp.), of 9-chloro-4-hydroxy-3-carbethoxy-p-phenanthroline (V) in 94% yield. In contrast to the corresponding compound in the unsubstituted p-phenanthroline

series this compound dissolves only in moderately strong hydrochloric acid, but, similarly, is insoluble in alkali.

To hydrolyse this ester it was refluxed for six hours with 20% methanolic potassium hydroxide and thus converted in 97% yield to 9-chloro-4-hydroxy-3-carboxy-p-phenanthroline, (VI), m.p. 310-315° with frothing. As will be seen it is very important that this acid should be completely free from traces of alkali salt and so purification was carried out by precipitating from dilute solution in sodium hydroxide by adding acetic acid till the pH was lowered to 4, followed by thorough washing of the precipitate.

Decarboxylation of this acid was successfully accomplished by refluxing in dry quinoline with copper-barium-chromite as catalyst or by heating the dry acid at 300° until frothing ceased. By both methods, 9-chloro-4-hydroxy-p-phenanthroline, (VII), m.p. 338-340°, was obtained.

Some difficulty was encountered in the quinoline method. This was traced to the presence of sodium salt of the acid. In using acid which contained some of this contaminant the yield of decarboxylated product was drastically reduced or sometimes the reaction did not occur to any detectable extent.

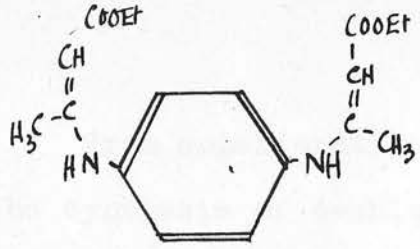
This experience is analogous with the findings of Lauer et al. (J.A.C.S., 68, 1268 (1946)) with 3-carboxy-4-hydroxy-6-chloro-8-methoxy-quinoline in diphenyl ether who report that even traces of the sodium salt completely altered the behaviour of this acid on decarboxylation.

Treatment of 9-chloro-4-hydroxy-p-phenanthroline, (VII) with phosphorus pentachloride and phosphoryl chloride at 140° for four hours yielded 4:9-dichloro-p-phenanthroline, (VIII), m.p. 225-226°. In general properties, this compound resembled the 4-chloro-p-phenanthroline already described.

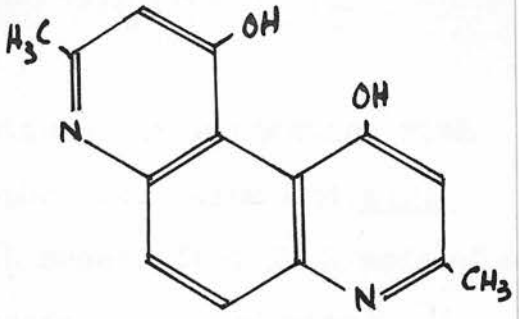
(3) The Synthesis of 4:5-dichloro-p-phenanthroline.

It is mentioned earlier, in the consideration of the possible dichloro-isomers which might result from the treatment of p-phenanthroline di-N-oxide with phosphoryl chloride, that one of these could be 4:5-dichloro-p-phenanthroline. It seemed therefore of some interest to attempt the preparation of this compound and having been exploring the use of ethoxymethylenemalonate with 6-amino-quinoline, it seemed therefore natural to extend the investigation to the use with p-phenylene diamine.

The preparation of 2:7-dimethyl-4:5-dihydroxy-p-phenanthroline has been described by Jacini (Gazetta, 1939, 69, 111-117) who heated p-phenylene diamine with two molcules of ethyl acetoacetate and obtained diethyl p-phenylene bis-β-aminocrotonate (I) which was doubly cyclised in mineral oil at 260° to give 2:7-dimethyl-4:5-dihydroxy-p-phenanthroline,(II).



(I)



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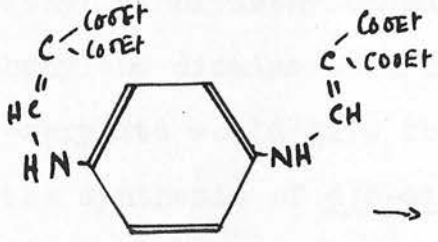

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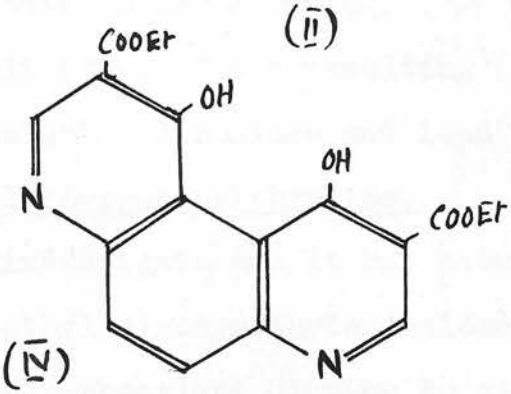

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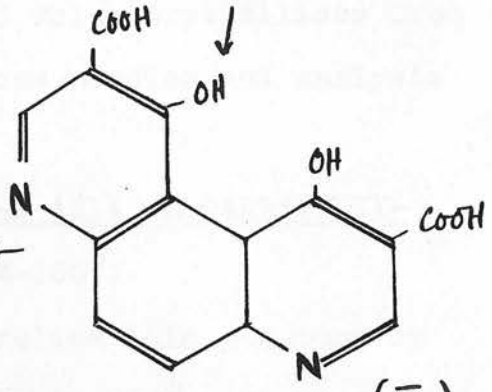

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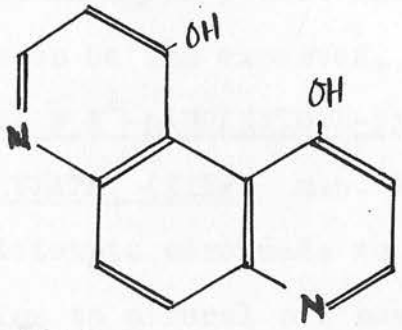

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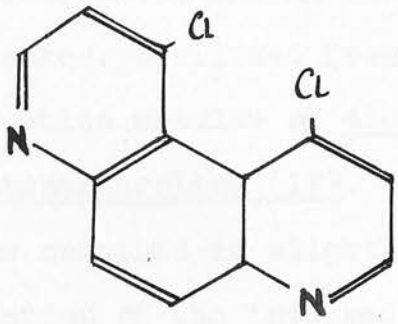

(VII)

From considerations mentioned in connection with the synthesis of 4-chloro-p-phenanthroline and 4:9:-dichloro-p-phenanthroline it seemed that if 2 molecules of ethyl ethoxymethylenemalonate condensed with p-phenylene diamine then cyclisation of the resulting bis-acrylate would give the angular structure and lead to the synthesis of 4:5-dichloro-p-phenanthroline, (VII). This route has been investigated and it has been found that two molecules of ethyl ethoxymethylenemalonate condense with one molecule of p-phenylene diamine to give a solid product, in 88% yield, which crystallises from ethanol in light-yellow fibrous needles and analysis proves to be the expected,

DIETHYL N,N'-p-PHENYLENE-BIS-β-AMINO-α-CARBETHOXY-ACRYLATE, (III). m.p. 164-165°.

Attempts were made to cyclise this compound by addition to mineral oil heated to 250° without success, much tar formed and no cyclised product was isolated. Addition, however, of the bis-acrylate to refluxing diphenyl was more successful and an 88% yield of a solid was obtained which recrystallised from ethanol or pyridine to give white needles of 4:5-dihydroxy-3-6-dicarbethoxy p-phenanthroline (IV).

This compound was obtained in slightly higher yield without the isolation of the intermediate bis-acrylate by adding 1 molecule of p-phenylene diamine and 2 molecules of ethyl ethoxymethylenemalonate to solid diphenyl and

heating the mixture to refluxing for forty-five minutes.

Hydrolysis of this ester (IV) with 20% methanolic potassium hydroxide for four hours yielded 4:5-dihydroxy-3:6-dicarboxy-p-phenanthroline (V). m.p. 297-298° (with frothing) in 70% of theory. It was found that the crude acid formed a gel on precipitation from dilute solution in alkali by the addition of acetic acid. After this treatment the purified acid, however, was precipitated as a solid from further solution in alkali.

This acid (V) was decarboxylated successfully either by refluxing in quinoline with copper-barium-chromite as catalyst, in 93% yield, or by heating the dry acid at 300° until frothing and liberation of carbon dioxide had ceased, in 85% yield, to give a solid which was recrystallised from water to give yellow needles of 4:5-dihydroxy-p-phenanthroline, (VI), m.p. 365-370° (decomp.).

This compound (VI) was heated under reflux with phosphoryl chloride and phosphorus pentachloride. After the bulk of phosphoryl chloride was removed, the residue was treated with ice water. When the base was precipitated by excess sodium hydroxide solution, no immediate turbidity resulted but after

(SEE NEXT PAGE)

two molecules of ethyl ethoxymethylenemalonate condense with one molecule of p-phenylene diamine to give a solid product, in 88% yield which crystallised from ethanol in light-yellow fibrous needles and

analysis proves to be the expected diethyl N,N^{1}-p-phenylene-bis- -amino- -carbethoxy-acrylate, (III), m.p. 164-165°. Attempts were made to cyclise this compound by addition to mineral oil heated to 250° without success, much tar formed and no cyclised product was isolated. Addition, however, of the bis-acrylate to refluxing diphenyl was more successful and an 88% yield of a solid was obtained which recrystallised from ethanol or pyridine to give white needles of 4:5-dihydroxy-3:6-dicarbethoxy-p-phenanthroline (IV). This compound was obtained in slightly higher yield without the isolation of the intermediate bis-acrylate by adding 1 molecule of p-phenylene diamine and 2 molecules of ethyl ethoxymethylenemalonate to solid diphenyl and heating the mixture to refluxing for forty-five minutes.

Hydrolysis of this ester (Iv) with 20% methanolic potassium hydroxide for four hours yielded 4:5-di-hydroxy-3:6-dicarboxy-p-phenanthroline (V), m.p. 297 - 298°, with frothing in 70% of theory. It was found that the crude acid in a few minutes a solid separated in yellow well-defined needles. When this crystalline product was recrystallised from ethanol it was obtained as yellow needles of 4:5-dichloro-p-phenanthroline (VIII), m.p. 247-248°. This compound was distinct in appearance and properties

from the 2:7-dichloro-p-phenanthroline, m.p. 315-316°, described above, a mixed sample giving a depression in melting-point.

C. PREPARATION OF AMINES FROM CHLORO-p-PHENANTHROLINES.

As is well-known chloro-atoms in positions 2 and 4 in pyridine and quinoline are usually readily replaced by aminoid reagents. Thus 2- or 4-chloro quinoline with aniline gives 2- or 4-anilino-quinoline. In the same way, a chloro-atom in the 2, 4, 5 or 7 position of p-phenanthroline shows a similar activity. Consequently it is not difficult to replace a chlorine atom in one of these positions of p-phenanthroline by a suitable amine. Reaction takes place when the chloro-p-phenanthroline and the primary amine are heated together. In the present work it was desired to introduce a dialkylamino-alkylamino group of the type present in mepacrine and the general procedure was to heat the chloro-compound along with an excess of the dialkylamino-alkylamine with or without a catalyst till the latter refluxed gently.

2-chloro-p-phenanthroline was heated with 2-diethylaminoethylamine for hours. After the excess of amine was removed the residual product went solid but was found to be hygroscopic and was taken up in ethanol, and ethanolic hydrobromic acid was added followed by a few drops of acetone. Cream solid was deposited and on recrystallisation from methanol gave cream plates, which analysis showed to

be the trihydrobromide of 2-diethylaminoethylamino-p-phenanthroline.

When 2-chloro-p-phenanthroline was similarly treated with 3-diethylaminopropylamine and the excess amine removed, the resulting product resembled the previous one and was worked up in a similar way. The hydrobromide separated without the addition of acetone, and the cream needles again proved to be the trihydrobromide.

2-chloro-p-phenanthroline was heated with 2-amino-5-diethylaminoethylamine. The excess of amine was removed and the residual syrup taken up in ethanol. The picrate was formed from this solution, by the addition of an ethanolic solution of picric acid. However, the purification of this salt proved unsuccessful as it was found impossible to purify by recrystallisation from any of the common organic solvents. The base was regenerated and converted to the 3:5-dinitrobenzoate which was crystallised from ethanol in yellow needles which analysis showed to be the tris-3:5-dinitrobenzoate.

Opportunity was taken during the present work to prepare the hitherto unknown 4-(4-diethylamino-1-methyl-butyl-amino)-p-phenanthroline, as it was thought to be especially desirable to test this

compound for antimalarial action. 4-chloro-p-phenanthroline was heated with 2-amino-5-diethylaminopentane at 180° for five hours. On removal of the excess amine, the resulting solid was drained from residual oil and after crystallisation from ethanol had melting-point 145-146° and this melting-point showed no depression on admixture with a specimen of 4-chloro-p-phenanthroline, m.p. 145-146°. A further experiment was carried out using re-distilled 2-amino-5-diethylaminopentane and a trace of copper powder and a minute crystal of iodine as catalysts. After heating for five hours at 180°, the excess amine was removed and the residual oil was dissolved in dilute hydrochloric acid, basified and taken into ether. Removal of the solvent yielded a brown oil which was converted to the 3:5-dinitrobenzoate in ethanol. Crystallisation of the product gave yellow needles which analysis proved to be the bis-3:5-dinitrobenzoate.

When 4:9-dichloro-p-phenanthroline was heated with 3-diethylaminopropylamine and the excess of base removed, the product which remained was purified by dissolving in dilute acid, basifying, and taking into ether. It was hoped that the base might crystallise, but it was found to remain liquid after standing for

12 hours. The base was therefore converted into the bis-3:5-dinitrobenzoate. This compound still contained chlorine and analysis showed this and the presence of one side-chain. Thus in a compound like 4:9-dichloro-p-phenanthroline, the 4-chloro-atom is capable of replacement while the chloro-atom in position 9 is stable.

D. Biological Results:

The main object of this research from the biological point of view was to synthesise certain derivatives of p-phenanthroline with basic side-chains in positions 2 and 4.

Of the compounds prepared the following three, the trihydrobromide of 2-(3-diethylaminopropylamino)-p-phenanthroline, trihydrochloride of 4-(4-diethylamino-1-methylbutylamino)-p-phenanthroline, and the trihydrochloride of 9-chloro-4-(4-diethylamino-1-methylbutylamino)-p-phenanthroline, were submitted to the Chemotherapy Committee of the Medical Research Council for biological tests and we are indebted to them for the following results.

For antimalarial action these compounds were tested on P. gallinaceum in chicks. Toxicity being first determined in mice. The toxic doses for the various compounds are as follows, in the same order, as mentioned above:- 40 mgm., 10 mgm., and 10 mgm. for 20 g. body weight, administered orally.

When the compounds were tested for antimalarial activity at doses approximating to the maximum tolerated dose, 2-(3-diethylaminopropylamino)-p-phenanthroline was found to possess slgith but doubtful activity, there being a substantial decrease in the percentage of cells parasitized after the third and fifth days. The two derivatives substituted in

in the 4 position showed unambiguous activity. The results obtained by Dr. Perry are presented in the following tables, control tests are added in each table.

9-Chloro-4-Diethylaminopropylamino-p-phenanthroline.

Dosage.	Day after infection and % parasitaemia.														
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10mg/20G	-	-	-	-	-	-	-	-	-	1%	1%	5%			
bdx4	-	-	-	-	-	-	-	1%	2%	50%	K				
oral.	-	-	--	-	-	-	-	-	-	-	--	-	-	-	-
Nil.	20%	25%	30%	D											
	-	-	2%	10%	80%	D									
	-	-	1%	5%	15%	D									
	-	-	1%	5%	8%	D									

4-(4-diethylamino-1-methylbutylamino)-p-phenanthroline.

Dosage.	Day after infection and% parasitaemia.															
	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10mg/20G	-	-	-	-	1%	1%	2%	5%	5%	10%	50%	70%	D			
bdx4	-	-	-	-	-	-	-	1%	1%	1%	2%	5%	10%	50%	80%	D
oral.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nil.	-	-	-	1%	5%	10%	30%	60%	80%	D						
	-	1%	1%	5%	10%	20%	10%	10%	50%	70%	D					
	-	-	-	-	1%	1%	2%	10%	50%	D						
	-	-	-	-	1%	2%	5%	30%	50%	70%	80%	D				

Repeat Test with 4-(4-diethylamino-1-methylbutylamino)-p-phenanthrol-ine.

Dosage.	Day after infection and % parasitaemia.														
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
10mg/20G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
bd x 4	-	-	-	-	-	-	-	-	-	1%	5%	50%	D		
oral.	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5mg/20G	-	-	-	-	-	-	-	1%	1%	5%	70%	D			
bd x 4	-	-	-	1%	2%	5%	10%	50%	60%	70%	D				
oral	-	-	-	-	1%	10%	20%	70%	D						
Nil.	20%	25%	30%	70%	D										
	-	-	2%	30%	80%	D									
	-	-	1%	5%	15%	70%	D								
	-	-	1%	2%	8%	50%	D								

These results are in interesting contrast with those previously obtained when 4-diethylaminopropylamino-p-phenanthroline was tested against P. relictum in canaries. The latter compound was found to be negative in that test. Both of the new compounds differ in ways which might be expected to affect the antimalarial activity, namely, the introduction of the 4-diethylamino-1-methylbutylamino-grouping and of the chloro-group. On the other hand, the difference may result from the different biological test used. This can only be settled by further experiments.

The relation of these compounds to the known antimalarials of the mepacrine and chloroquine types has been discussed in the Introduction and their activity confirms the general line of argument therein.

In addition to the antimalarial tests, 9-chloro-4-(3-diethylamino-1-methylbutylamino)p-phenanthroline was submitted to an invitro test against amoebae and was found to be active at a dilution of 1 in 100,000

III. EXPERIMENTAL.

p- PHENANTHROLINE.

(cf. B.P. 394,416 Modified Skraup Reaction
HALCROW and KERMACK, J.C.S., 1946, 155).

p- phenylene diamine (30 g.) was added in portions, as rapidly as convenient, to 69% sulphuric acid (655.5 c.c.) with cooling, as necessary. A mixture of 80% aqueous arsenic acid (166.6 c.c.) and 90% aqueous glycerol (142.6 c.c.) - it is convenient to mix these reagents to facilitate the transferance of the glycerol - were then added and the solution was heated under reflux for 2½ hours, when a diazo test was negative. The solution was diluted with water (1000 c.c.) and ammonia (S.G. 0.88) added carefully with stirring until the solution was alkaline to litmus. Some dark brown material separated from the cold mixture and was collected by filtration and retained. The filtrate was extracted hot with hot benzene four times (1000 c.c. and three 500 c.c. portions). The solid collected from the alkaline solution was also extracted with hot benzene and the combined extracts were concentrated to 400 c.c. (approx.) and allowed to crystallise to yield light-brown material (30 g.) M.P. 171-2°. Further material (15 g.) M.P. 165-7° was obtained by concentration of the benzene mother liquors. Re-crystallisation from benzene using charcoal, yielded

white needles (40 g. 80% yield on theory) M.P. 172-3°. Literature M.P. 173° (Skraup and Vortmann).

Purification was attempted by vacuum distillation of the crude product but the product was a yellow waxy material M.P. 145-150° which on redistillation gave material M.P. 148-154°, after two days standing over sulphuric acid in an evacuated desiccator. This method was abandoned in favour of recrystallisation from benzene.

PERBENZOIC ACID.

(cf. TIFFENEAU, ORGANIC SYNTHESIS, COLL. VOL. I (1st Ed.) p. 422).

A solution of pure, dry, finely powdered benzoyl peroxide (121 g.) M.P. 104° in dry toluene (1500 c.c.) was placed in a 5 l. round-bottomed flask fitted with a mechanical stirrer and surrounded by an ice-salt freezing mixture, and the temperature adjusted to below -5°.

A solution of sodium ethoxide was prepared by adding sodium (23 g.) to absolute ethanol (500 c.c.) with cooling. The temperature of this solution was adjusted to 0° and added from a dropping funnel to the well-stirred toluene solution, which whitened and thickened due to the formation of sodium perbenzoate. Ice-water (2000 c.c.) was added to the stirred mixture until clarification was complete. The toluene layer was separated in a previously cooled separating funnel and discarded. The aqueous layer was extracted with ether (one 500 c.c. portion) and replaced in the original flask surrounded by a freezing mixture and the temperature adjusted to 0°.

Sulphuric acid (54 g. S.G.1·84) was added to water (50 c.c.), cooled and slowly added from the dropping funnel to the well-stirred solution, which became turbid due to suspended white oil. The

mixture was transferred to a cooled separating funnel and extracted with cold chloroform (three 250 c.c. portions) and the extract dried over anhydrous sodium sulphate for two hours.

The perbenzoic acid content of the chloroform extract was determined by mixing 1 c.c. of the solution, 3 drops of dilute hydrochloric acid, potassium iodide (1 g.) and titrating the liberated iodine with standard sodium thiosulphate and using starch solution as indicator.

The average yield obtained from two preparations was 18 g. of perbenzoic acid, which is 40% of theory.

p- PHENANTHROLINE N-OXIDE.

(cf. KERMACK and TEBRICH, J.C.S., 1945, 375).

p- Phenanthroline (10 g. M.P. 172°) was kept in an evacuated desiccator for 24 hours and then dissolved in dry chloroform (60 c.c.), and mixed with a solution of perbenzoic acid (8 g.) in chloroform (420 c.c.). The mixture was kept at 0° for 24 hours and the solvent removed under reduced pressure on the water bath to leave a yellow solid which was extracted with 2N-hydrochloric acid (four 10 c.c. portions). The combined acid extracts were rendered alkaline with 10 N- sodium hydroxide solution and extracted with chloroform. On removal of the solvent, it was found that the melting point of the residual solid gradually rose with successive extracts. The first six extracts yielded 4.5 g. material M.P. 200-210°, which on recrystallisation two times from ethanol yielded white needles of p- phenanthroline N-oxide M.P. 233-234° (3.5 g. 32% of theory). (Found: C, 73.8; H, 4.2. $C_{12}H_8N_2O$ requires C, 73.5; H, 4.1%).

On working up the mother liquors from these crystallisations a cream crystalline solid (1.6 g.) M.P. 176-180° was obtained, which gave no depression on admixture with a specimen of p- phenanthroline.

Further chloroform extracts of the alkaline

solution on removal of the solvent yielded orange-yellow solid (2 g.) M.P. 270-280° which recrystallised from hot water to give a small amount of cream-white needles M.P. 323-324°. This material gave no depression in melting point on admixture with a specimen of p-phenanthroline di-N-oxide prepared as described below.

p-PHENANTHROLINE N-OXIDE is soluble in dilute mineral acid and insoluble in alkali. It is moderately soluble in cold water, ethanol, chloroform and benzene and insoluble in light petroleum 100/120°. An aqueous solution gives no colour with ferric chloride solution.

p- PHENANTHROLINE DI-N-OXIDE.

Dry p- phenanthroline (10 g. M.P. 172°) was dissolved in chloroform (60 c.c.) and mixed with a solution of perbenzoic acid (12 g.) in chloroform (1030 c.c.). After standing for two days at 0°, pale yellow needles had separated and were collected, drained, washed with a little fresh chloroform and dried (11 g. M.P. 320-321°). The chloroform filtrate was taken to dryness in a vacuum on the water-bath to yield a yellow solid residue which was extracted three times with 2 N-hydrochloric acid (10 c.c. portions). The acid extract was made alkaline with 10 N-sodium hydroxide solution and extracted with chloroform. Removal of the chloroform in a vacuum left solid material (0.2 g.) M.P. 309-310°. The total crude product was recrystallised from hot water yielding white needles (8.8 g., 75% yield) M.P. 324-325°, of p- phenanthroline di-N-oxide. (Found: C, 68.3; H, 4.1; N, 13.7. Calc. for $C_{12}H_8O_2N_2$: C, 67.9; H, 3.8; N, 13.2%).

As mentioned in the theoretical section Linsker and Evans prepared a compound with melting point 308° which they consider to be p- PHENANTHROLINE DI-N-OXIDE.

p- PHENANTHROLINE DI-N-OXIDE is soluble in

dilute mineral acid, insoluble in cold and moderately soluble in hot water, insoluble in alkali and most of the common organic solvents in the cold. No colour is obtained with ferric chloride solution.

TREATMENT OF p-PHENANTHROLINE N-OXIDE WITH PHOSPHORYL CHLORIDE.

Phosphoryl Chloride (3 c.c.) was added to dry p-phenanthroline N-oxide (1 g. M.P. 232-233°) with the liberation of much heat for 2-3 minutes, some solid remaining undissolved. The mixture was refluxed for one hour before the solid dissolved completely to give a muddy-brown solution and the refluxing continued for one further hour. The excess phosphoryl chloride was removed in a vacuum and the (residual) greyish syrup treated with cold water (25 c.c.) to decompose any phosphoryl chloride. The resulting yellow solution was rendered alkaline with 10 N-sodium hydroxide solution when a greyish white solid was deposited. After being left to stand for 24 hours the solid was collected, drained, washed with a little fresh water and dried (0.6 g.) M.P. 150-160°. Recrystallisation from ethanol yielded white needles of 2-chloro-p-phenanthroline (0.3 g., 30% of theory) M.P. 190-191°, whose melting point was not depressed on admixture with a specimen of 2-chloro-p-phenanthroline M.P. 190-191° prepared by the other method described below.

2-CHLORO-p-PHENANTHROLINE was found to be soluble in dilute mineral acid, insoluble in alkali and practi-

cally insoluble in cold water. It is soluble in ethanol and benzene and moderately soluble in light petroleum 100/120° in the cold.

TREATMENT OF p-PHENANTHROLINE DI-N-OXIDE WITH PHOSPHORYL CHLORIDE.

Phosphoryl chloride (24 c.c.) was added to dry p-phenanthroline di-N-oxide (2 g. M.P. 324-325°) with the liberation of heat. After about 30 minutes the whole of the material was in solution. The mixture was refluxed for five hours to give a grey syrupy solution from which the excess phosphoryl chloride was removed at 100° under reduced pressure. A little ice water was added to the residual syrup and the resulting white solid suspension dissolved in 11 N-hydrochloric acid (40-50 c.c.) to give a muddy-brown solution, which was filtered and rendered alkaline with 10 N-sodium hydroxide solution to precipitate whitish material, which was collected, drained, washed with a little fresh water, and dried (M.P. 240-250°). Prolonged extraction (1 day) of this material with hot ethanol yielded 1 g. of material M.P. 300-310°, which on recrystallisation from ethanol yielded 0.2 g. of 2:7 dichloro-p-phenanthroline M.P. 315-316°. (Found: C, 58.3; H, 2.8. $C_{12}H_6N_2Cl_2$ requires C, 57.8; H, 2.4%). No depression of the melting point was obtained on admixture with a specimen of 2:7 dichloro-p-phenanthroline M.P. 315-316° prepared by the method described below.

This compound is soluble in dilute mineral acid, insoluble in cold water and alkali. Soluble in ethanol and benzene and sparingly soluble in light petroleum 100/120° in the cold.

p-PHENANTHROLINE METHIODIDE.

p-phenanthroline (25 g.) was dissolved in nitrobenzene (250 c.c.) and methyl iodide (100 c.c.) added. The solution was heated under reflux on the water-bath for 2 hours. The colour of the solution changed to red and yellow needles were deposited during the heating. On cooling a further quantity separated. The combined products were recrystallised from water (in which it is only moderately soluble in the cold) to give yellow needles (38 g., 84% yield) M.P. 270-271°, of p-phenanthroline methiodide. Sparingly soluble in ethanol and methanol in the cold.

1 - METHYL - p-PHENANTHROL-2-ONE.

(cf. HALCROW and KERMACK, J.C.S., 1946, 155).

p-Phenanthroline methiodide (38 g.) was dissolved in water (2100 c.c.) and small portions added alternately with small portions of a sodium hydroxide solution (17.7 g. in 422 c.c. water) to a solution of potassium ferricyanide (92.4 g.) in water (844 c.c.). The mixture was set aside for 1½ hours and then made strongly alkaline by the addition of 10 N-sodium hydroxide solution (1050 c.c.) to precipitate a yellow solid which was collected, drained and dried in a vacuum. Recrystallisation from benzene yielded yellow needles (23 g., 92% of theory) M.P. 243-244°, of 1-methyl-p-phenanthrol-2-one.

This compound was soluble in dilute mineral acid, moderately soluble in cold water and insoluble in strongly alkaline solution.

2 - CHLORO-p-PHENANTHROLINE.

(cf. KERMACK and WEBSTER, J.C.S., 1942, 213.
cf. HALCROW and KERMACK, J.C.S., 1946, 155.)

1 - Methyl-p-phenanthrol-2-one (4 g.) was mixed with phosphorus pentachloride (5 g.) and phosphoryl chloride (30 c.c.) and heated for five hours at 150° in a sealed tube. Excess phosphoryl chloride was removed at 100° under reduced pressure and the product treated with a little ice water. The resulting solution was rendered alkaline with ammonia to precipitate a pinkish solid. This solid was collected, drained, washed with a little fresh water and dried (2.5 g.) M.P. 186-188° and was recrystallised from ethanol to yield white needles (2.2 g.) M.P. 190-191° of 2-chloro-p-phenanthroline.

This compound had properties similar to those shown by the compound already described prepared from p-phenanthroline N-oxide with which there was no depression of the melting point.

2 - KETO-1-METHYL-1:2-DIHYDRO-p-PHENANTHROLINE METHIODIDE.

1 - Methyl-p-phenanthrol-2-one (0.6 g.) was dissolved in nitrobenzene (10 c.c.) and methyl iodide (4 c.c.) added. The mixture was heated under reflux for 8 hours on the water-bath and yellow crystals were deposited, and were collected, drained, washed with a little fresh nitrobenzene and dried (1 g., 73% of theory) M.P. 289-290°. Recrystallisation from methanol yielded yellow needles (0.8 g.) M.P. 290-291° of the methiodide of 2 - keto-1-methyl-1:2-dihydro-p-phenanthroline. (Found: C, 47.9; H, 3.9. $C_{14}H_{13}N_2I$ requires C, 47.7; H, 3.7%).

Soluble in cold water, sparingly soluble in methanol, and acetone in the cold. Insoluble in benzene in the cold.

2:7 - DIKETO- 1:8 - DIMETHYL - 1:2:7:8 - TETRAHYDRO - p-PHENANTHROLINE.

2 - Keto-1-methyl-1:2-dihydro-p-phenanthroline methiodide (6.7 g.) was dissolved in water (36 c.c.) and small portions of the solution added alternately with small portions of a sodium hydroxide solution (0.3 g. in 7.2 c.c. water) to a solution of potassium ferricyanide (1.6 g.) in water (15 c.c.). During the addition the colour of the solution changed from greenish to russet-red and after standing at room temperature for 15 minutes reddish-orange crystals were deposited; the mixture was set aside for a further 15 minutes then the crystals, M.P. 350-360°, were collected and the filtrate rendered alkaline with 10-N-sodium hydroxide solution (18 c.c.) to precipitate a little more of the reddish-orange solid, M.P. 350-360°. The combined products (0.45 g., 89% yield) were re-crystallised from water to give yellow needles (0.4g.) M.P. 363-364°, of 2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-p-phenanthroline.

(Found: C, 67.0; H, 5.1; N, 11.3.
$C_{14}H_{12}O_2N_2$, $\frac{1}{2}H_2O$ requires C, 67.5; H, 5.2; N, 11.2%).

This compound was soluble in strong hydrochloric acid but not in alkali, and was sparingly soluble in ethanol and acetone in the cold.

2:7-DICHLORO-p-PHENANTHROLINE.

2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-p-phenanthroline (0.2 g.) was mixed with phosphorus pentachloride (1 g.) and phosphoryl chloride (3 c.c.) and heated in a sealed tube for 24 hours at 150°. On opening the tube the solution was found to be dark in colour with whitish crystals throughout. The excess phosphoryl chloride was decomposed by drops of ice water and the solution was made strongly alkaline with 10 N-sodium hydroxide solution to precipitate a greyish white solid, which was collected, drained, washed with a little fresh water to remove inorganic phosphate and dried in a vacuum. This product was extracted with hot ethanol, the insoluble material being filtered off. The extract was concentrated to a few c.c's and allowed to crystallise to yield white needles, M.P. 310-311°. Further crystallisation from ethanol yielded white needles, M.P. 315-316°, of 2:7-dichloro-p-phenanthroline. (Found: C, 53.6; H, 2.7; N, 10.1. $C_{12}H_6N_2Cl_2$, H_2O requires C, 53.9; H, 3.0; N, 10.5%).

When larger quantities of 2:7-diketo-1:8-dimethyl-1:2:7:8-tetrahydro-p-phenanthroline were treated with phosphorus pentachloride and phosphoryl chloride in exactly the same proportions as in the

small experiment just recorded most of the compound was recovered unchanged after heating at 150° for 24 hours and it was then found ~~that~~ in 6 g. and 8 g. experiments that most of the compound had been converted to 2:7-dichloro-p-phenanthroline by heating at 172° for 86 hours but even after this vigorous treatment some of the unchanged compound was recovered.

DIETHYL ETHOXYMETHYLENEMALONATE.

(cf. CLAISEN, ANN., 1897, 297, 75.

BER., 1893, 26, 2731.

WHEELER and JOHNS., AMER. CHEM. J. 40, 233 (1908).

FUSON, PARHAM and REED, J. ORG. CHEM., 11, 194 (1946).

The details of this method of preparation were kindly supplied by Imperial Chemical Industries Ltd. (Dyestuffs Division).

Diethyl malonate (120 c.c.), ethyl orthoformate (133 c.c.), acetic anhydride (153 c.c.) and powdered anhydrous zinc chloride (9 g.) were heated together in a 500 c.c. two-necked flask, fitted with a thermometer and reflux condenser, in an oil bath until refluxing begins. The reaction started at 90-100° internal temperature and the oil-bath was removed when the reaction became vigorous. When the reaction subsided (15-30 mins.) the reflux condenser was replaced by a fractionating column and condenser set for distillation. Heating was continued for ten hours at 110°, internal temperature. Ethyl acetate slowly distilled off during this period. The cold reaction mixture was filtered to remove zinc salts

and the filtrate distilled in a vacuum using a fractionating column. The first fraction obtained was a mixture of the volatile constituents, acetic anhydride, acetic acid, ethyl acetate and ethyl orthoformate, (140 g.) at 60°/60-70 m.m., the second fraction (54 g.) at 76°/10 mm. consisted of diethyl-malonate, and third fraction (60 g.) (57% of theory) at 150°/10 mm. was diethyl ethoxymethylene malonate. A non-volatile residue was obtained which solidified on rubbing with ether. The solid recrystallised from light petroleum in colourless needles, m.p. 94-95°, and appeared to be 3:5-dicarbethoxy-6-ethoxy-α-pyrone (cf. Theoretical Section).

ETHYL β-6'-QUINOLYL-AMINO-α-CARBETHOXY-ACRYLATE.

(cf. CLAISEN, ANN., 1897, 297, 75.
BER., 1893, 26, 2731).

Diethyl ethoxymethylenemalonate (2 c.c.) and 6-amino-quinoline (1 g.) were heated on the boiling water-bath for 45 minutes during which time any ethanol formed was removed in a vacuum. The product was a brown syrup which on cooling solidified to a whitish solid, which was collected and pressed out to remove any ethanol and washed with a small quantity of light petroleum 60/80° and dried to give a white solid (2 g., 95% of theory), m.p. 88-90°. This product was recrystallised from ethanol to yield large white rectangular plates, m.p. 97-98°, of ethyl β-6'-quinolyl-amino-α-carbethoxy-acrylate.

(Found: C, 65.1; H, 5.7; N, 8.8.
$C_{17}H_{18}O_4N_2$ requires C, 65.0; H, 5.7; N, 8.9%).

This acrylate is soluble in dilute mineral acid, insoluble in cold water and alkali. Soluble in acetone, ether, and benzene in the cold.

4-HYDROXY-3-CARBETHOXY-p-PHENANTHROLINE.

(cf. LIMPACH, BER., 64, 969 (1931)).

Ethyl β-6'-quinolyl-amino-α-carbethoxy-acrylate (9 g.), m.p. 88-90°, was added in small portions with efficient stirring during 15 minutes to mineral oil (180 c.c.), preheated to 250-260°. The temperature was maintained for a further 15 minutes. On cooling yellowish-brown solid separated from the reaction mixture, which was filtered and the collected solid drained and washed well with light petroleum 60/80° to remove traces of the oil and dried to give a brown material (7.0 g., 91% of theory), m.p. 265-270°. This product was recrystallised, using charcoal, from ethanol to yield colourless rectangular prisms, m.p. 285-286°, of 4-hydroxy-3-carbethoxy-p-phenanthroline. (Found: C, 66.9; H, 4.6; N, 10.2. $C_{15}H_{12}O_3N_2$ requires C, 67.2; H, 4.5; N, 10.45%).

This is soluble in dilute mineral acid, insoluble in water and alkali. Insoluble in benzene, hot and cold.

4-HYDROXY-3-CARBOXY-p-PHENANTHROLINE.

4-hydroxy-3-carbethoxy-p-phenanthroline (16 g.) m.p. 265-270°, was mixed with 20% methanolic potassium hydroxide (160 c.c.) and refluxed on the water-bath for 6 hours. The reaction mixture was diluted with water (350 c.c.) and the dark brownish-red solution treated with charcoal, and made acid with glacial acetic acid to deposit a cream-coloured solid. This product was collected, drained, washed with a little fresh water and dried (13 g., 91% of theory), m.p. 270-280° (with frothing). Purification of this material was achieved by dissolution in dilute ammonia (2N), treatment of the solution with charcoal, and re-precipitation with 2N-acetic acid to yield, after three treatments cream micro-needles, m.p. 307-308°, with frothing, of 4-hydroxy-3-carboxy-p-phenanthroline.

(Found: C, 60.4; H, 4.2; N, 10.4.
$C_{13}H_8O_3N_2$, H_2O requires C, 60.5; H, 3.9; N, 10.85%).

This acid is soluble in dilute mineral acid and in alkali, insoluble in hot and cold water; practically insoluble in the common organic solvents.

4-HYDROXY-p-PHENANTHROLINE.

(cf. KERMACK and WEATHERHEAD, J.C.S., 1940, 1164.)

METHOD A.

4-hydroxy-3-carboxy-p-phenanthroline (11 g.) m.p. 270-280° with frothing, was mixed with copper-barium-chromite catalyst (0.1 g.) and added to dry, redistilled quinoline (220 c.c.). The mixture was refluxed for 45 minutes. The mixture cooled to 100° was filtered from the catalyst. The quinoline was removed by steam-distillation and the resulting aqueous solution evaporated to dryness on the water-bath to yield a brownish solid residue (8 g., 88% of theory) m.p. 275-280°. This material was re-crystallised, using charcoal, from boiling water to yield fibrous needles, m.p. 300-301°, of 4-hydroxy-p-phenanthroline.

(Found: C, 68.5; H, 4.2; N, 13.15. Calculated for $C_{12}H_8ON_2$, $\frac{3}{4}H_2O$: C, 68.7; H, 4.5; N, 13.4%).

A mixed melting-point determination with a specimen, m.p. 298°, prepared by Kermack and Weather-head (loc. cit.) from 6-amino-4-hydroxy-quinoline by a Skraup reaction, showed no depression. For their compound Kermack and Weatherhead give the following analytical figures:- Found: C, 70.5; H, 4.6. $C_{12}H_8ON_2$, $\frac{1}{2}H_2O$ requires C, 70.2; H, 4.4%.

METHOD B.

4-Hydroxy-3-carboxy-p-phenanthroline (1 g.), m.p. 270-280° with frothing, was heated in a dry test-tube in a Wood's metal-bath, to 300°, and the temperature maintained for a few minutes until the frothing ceased. The solid black residue (0.7 g., 84% of theory) was extracted with boiling water several times (3 x 50 c.c.) and the combined extracts were concentrated to about 30 c.c. to obtain yellow needles, m.p. 298-300°, which crystallised from water in pale yellow fibrous needles, m.p. 300-301°, of 4-hydroxy-p-phenanthroline. Mixed melting-point determination with a specimen prepared by Kermack and Weatherhead and a specimen prepared by Method B, showed no depression.

4-CHLORO-p-PHENANTHROLINE.

(cf. KERMACK and WEATHERHEAD, J.C.S., 1940, 1164.)

4-hydroxy-p-phenanthroline (5 g.), m.p. 300-302°, phosphorus pentachloride (5 g.) and phosphoryl chloride (50 c.c.) were heated together under reflux for 3 hours at 130°. The excess phosphoryl chloride was removed at 100° under reduced pressure and the residual phosphoryl chloride decomposed by the careful addition of ice water. The resulting solution was treated with charcoal and made alkaline with 10N-sodium hydroxide solution to precipitate whitish-grey material, which was collected, drained, washed with a little water and dried (5 g., 90% of theory) m.p. 145-146°. Recrystallisation from water yielded white felted needles, m.p. 146-147°, of 4-chloro-p-phenanthroline.

This compound shows similar properties to those described by Kermack and Weatherhead (loc. cit.) who report the melting-point of their compound as 147°.

DIETHYL N,N'-p-PHENYLENE-BIS-β-AMINO-α-CARBETHOXY-ACRYLATE.

p- phenylene diamine (5 g.) and diethyl ethoxymethylene-malonate (23 c.c.) were heated on the boiling water-bath for 30 minutes, the alcohol being removed during the reaction under reduced pressure. The product, which had solidified after 10 minutes of heating, was collected, pressed and drained well, washed with a little light petroleum 60/80° and dried to give a yellow solid (17 g., 85% of theory) m.p. 160-164°. Recrystallisation, using charcoal, from ethanol yielded light yellow fibrous needles, m.p. 164-165°, of diethyl N,N'-p-phenylene-bis-β-amino-α-carbethoxy-acrylate.

(Found: C, 59.0; H, 6.3; N, 6.3.

$C_{22}H_{28}O_8N_2$ requires C, 58.9; H, 6.25; N, 6.25%).

This acrylate is insoluble in acid, alkali and water. Soluble in benzene in the cold.

4:5-DIHYDROXY-3:6-DICARBETHOXY-p-PHENANTHROLINE.

METHOD A.

Diethyl N,N'-p-phenylene-bis-β-amino-α-carbethoxy-acrylate, 17 g.) m.p. 160-164°, was added in small amounts in 10 minutes to refluxing diphenyl (170 g.) and the refluxing continued for a further 40 minutes. The reaction mixture was cooled to 60-70° and diluted with light petroleum 80/100° (400 c.c.) which had been heated to 70-80°. The deposited solid was collected by filtration and extracted with boiling light petroleum 80/100° for 5 hours to remove traces of diphenyl.

Drying of the extracted solid yielded a light-brown product (12 g.) (88% of theory) m.p. 255-260°.

METHOD B.

p-phenylene diamine (5 g.) and diethyl ethoxymethylenemalonate (23 c.c.) were added to diphenyl (170 g.) and refluxed for 45 minutes. The product was isolated as described in Method A to yield crude 4:5-dihydroxy-3:6-dicarbethoxy-p-phenanthroline (13.2 g., 97% of theory), m.p. 255-260°. Recrystallisation from ethanol or aqueous pyridine yielded short white needles, m.p. 278-280°

(further drying 283-284°), of 4:5-dihydroxy-3:6-dicarbethoxy-p-phenanthroline.

(Found: C, 57.8; H, 4.8; N, 7.95.

$C_{18}H_{16}O_6N_2$ requires C, 57.75; H, 4.8; N, 7.5%).

This ester is soluble in dilute mineral acid, insoluble in alkali and water in the cold. Insoluble in benzene and light petroleum 100/120° in the hot.

4:5-DIHYDROXY-3:6-DICARBOXY-p-PHENANTHROLINE.

4:5-dihydroxy-3:6-dicarbethoxy-p-phenanthroline, (10 g.) m.p. 255-260°, was added to 20% ethanolic potassium hydroxide (100 c.c.) and refluxed on the water-bath for four hours. The clear red-coloured solution was diluted with water (200 c.c.), treated twice with charcoal, and glacial acetic acid added to adjust the pH of the solution to 5. A yellow solid was deposited and allowed to stand for two hours. It was then collected, drained, washed with a little fresh water and dried at 90° to yield a brownish-yellow solid product (6 g., 70% of theory), m.p. 294-295° (frothing). Purification was achieved by dissolving the solid in the minimum quantity of dilute ammonia (2N) and, after treating the solution with charcoal, re-precipitating with acetic acid (2N). This treatment was carried out three times to yield brown micro-needles, m.p. 297-298°, with frothing, of 4:5-dihydroxy-3:6-dicarboxy-p-phenanthroline. (Found: C, 50.1; H, 3.3; N, 8.4. $C_{14}H_8O_6N_2$, H_2O requires C, 50.0; H, 3.6; N, 8.3%).

This acid is soluble in dilute mineral acid and in alkali and insoluble in hot water. Insoluble in most of the common organic solvents.

4:5-DIHYDROXY-p-PHENANTHROLINE.

(cf. KERMACK and WEATHERHEAD, J.C.S., 1940, 1164.)

METHOD A.

4:5-dihydroxy-3:6-dicarboxy-p-phenanthroline (10.3 g.) m.p. 294-295°, was mixed with copper-barium-chromite catalyst (0.1 g.) and added to dry, redistilled quinoline (200 c.c.) preheated to 150°. The mixture was refluxed for 1 hour, cooled to 100° and filtered to remove the catalyst. The filtrate was concentrated under reduced pressure to a volume of 50 c.c. and when cold, diluted with diethyl ether (500 c.c.) to deposit a brown solid. This product was collected, drained, and washed thoroughly with fresh ether to remove the quinoline completely, and dried (6.8 g., 93% of theory), m.p. 345-350° (frothing). This crude material was extracted with a large volume of boiling water; the extract treated with charcoal and concentrated to about 50 c.c. and allowed to crystallise to yield yellow needles, m.p. 365-370° (decomp.) of 4:5-dihydroxy-p-phenanthroline.

(Found: C, 66.0; H, 3.9; N, 12.0.
$C_{12}H_8O_2N_2\ \frac{1}{4}H_2O$ requires C, 66.5; H, 3.9; N, 12.9%).

This compound is soluble in moderately strong hydrochloric acid, and soluble in alkali, and insoluble in most of the common organic solvents.

METHOD B.

4:5-dihydroxy-3:6-dicarboxy-p-phenanthroline (1 g.) m.p. 294-295°, was heated evenly in a dry test-tube in a metal-bath (300°) until the frothing ceased. The black residue was treated with dilute ammonia (2N) to remove any unchanged acid, washed with small portions of water until free from alkali and dried to give a black product (0.6 g., 85% of theory) m.p. 340-350°. Recrystallisation was carried out as described in Method A to give 4:5-dihydroxy-p-phenanthroline, m.p. 365-370° (decomp.).

4:5-DICHLORO-p-PHENANTHROLINE.

4:5-dihydroxy-p-phenanthroline (6.5 g.) m.p. 350°, phosphorus pentachloride (13 g.) and phosphoryl chloride were heated together under reflux for 7 hours at 140° by which time solution was complete. Excess of phosphoryl chloride was removed in a vacuum on the water-bath and the residual syrup treated with ice water to give a yellow solution, which was filtered, treated with charcoal, and rendered alkaline with 10N-sodium hydroxide solution. Yellow needles crystallised, were collected, washed with fresh water and dried (4.3 g., 57% of theory) m.p. 235-240°. Recrystallisation from ethanol yielded yellow needles, m.p. 247-248°, of 4:5-dichloro-p-phenanthroline.

(Found: C, 57.8; H, 2.7; N, 11.3.
$C_{12}H_6N_2Cl_2$ requires C, 57.8; H, 2.4; N, 11.3%).

Very sparingly soluble in water.

ETHYL β-ANILINO-α-CARBETHOXY-ACRYLATE.

(cf. CLAISEN, ANN., 1897, 297, 1.

SCHOFIELD and SIMPSON, J.C.S., 1940, 1033.)

Aniline (4.3 g.) was mixed with diethyl ethoxymethylenemalonate (10 g.) and heated on the boiling water-bath for 30 minutes. The ethanol liberated was removed in a vacuum and the oily product solidified on scraping and standing (11 g., 90% of theory) m.p. 40-50°. Recrystallisation of this solid from light petroleum 40/60° yielded large clear platelets, m.p. 45-47°, of ethyl β-anilino-α-carbethoxy-acrylate.

(Found: C, 63.9; H, 6.5; N, 5.55.

Calculation for $C_{14}H_{17}O_4N$ ~~requires~~ C, 63.9; H, 6.5; N, 5.3%).

Although Claisen obtained this acrylate in solid form, m.p. 45-46°, Schofield and Simpson report that they were unable to obtain any crystalline material from the crude oily product.

6-NITRO-8-CHLOROQUINOLINE.

(cf. B.P. 394, 416.)

2-chloro-4-nitraniline (43 g.) was added to a mixture of concentrated sulphuric acid (166.7 c.c.) and water (130 c.c.) in a 2-litre bolthead flask. Glycerol (66.7 c.c.) and arsenic acid (73.7 c.c., 65% As_2O_5 solution) were added and the mixture gradually heated on a gauze to the boil. After refluxing gently for 3 to 4 hours (i.e. until the diazo test for unchanged amine was negative), it was poured into its own volume of water and rendered alkaline with 10N-sodium hydroxide solution with stirring. The addition of the sodium hydroxide solution caused first the precipitation of bright-yellow 6-nitro-8-chloro-quinoline sulphate, but as the medium became alkaline the colour changed to brownish grey. The 6-nitro-8-chloroquinoline was filtered off, washed till neutral and recrystallised from 65% aqueous ethanol (30 g., 54% of theory), M.P. 153-154°.

6-AMINO-8-CHLORO QUINOLINE.

(cf. WEST, J.C.S., 1925, 127, 494).

6-nitro-8-chloro-quinoline (83.4 g.) was heated to boiling with methylated spirit (225 c.c.) and concentrated hydrochloric acid (5 c.c.). Iron filings (69 g.) were added in portions over half-an-hour. The mixture was kept boiling vigorously to prevent caking. After two hours the acid was neutralised with 10N-sodium hydroxide solution, filtered hot and the residue well washed with hot spirit. The alcohol was distilled off on the water-bath and the residue recrystallised from benzene (65 g., 92% of theory) M.P. 154°.

ETHYL β-(8'-CHLORO-6'-QUINOLYL)-AMINO-α-CARBETHOXY-ACRYLATE.

(cf. CLAISEN, ANN, 1897, 297, 75.
BER., 1893, 26, 2731).

Diethyl ethoxymethylenemalonate (10 c.c.) was added to 6-amino-8-chloro-quinoline (5 g.) and heated on a boiling water-bath. Almost immediately ethanol was produced and was removed in a vacuum. After 30 minutes the reaction mixture solidified and the heating was continued for a further 30 minutes. The brownish solid was pressed out on a Buchner funnel, drained to remove any traces of ethanol, washed with a small quantity of light petroleum 60/80° and dried to give a reddish-brown product (9.2 g., 94% of theory) M.P. 136-140°. Recrystallisation from ethanol yielded yellow-orange needles, M.P. 141-142°, of ethyl β-8'-(chloro-6'-quinolyl)-amino-α-carbethoxy-acrylate.

(Found: C, 58.2; H, 4.9; N, 8.1.
$C_{17}H_{17}O_4N_2Cl$ requires C, 58.5; H, 4.9; N, 8.0%).

This acrylate is soluble in dilute mineral acid, ethanol and benzene in the cold, insoluble in water and alkali and light petroleum 100/120°.

A solution of the acrylate in dilute hydrochloric acid on treatment with sodium nitrite solution and β-naphthol in sodium hydroxide solution gave no colouration.

9-CHLORO-4-HYDROXY-3-CARBETHOXY-p-PHENANTHROLINE.

(cf. LIMPACH, BER., 64, 969, (1931)).

Ethyl β-(8'-chloro-6'-quinolyl)-amino-α-carbethoxy-acrylate (9.2 g.) M.P. 136-140°. was added in small portions with efficient stirring during 10 minutes to mineral oil (150 c.c.), heated to 250°. The temperature was maintained for a further 5 minutes during which time yellow-brown solid was deposited, and a little sublimate appeared in the colder upper surface of the containing beaker. The reaction mixture was cooled and filtered. The collected brown solid was well drained, washed well with light petroleum 60/80° to remove all traces of mineral oil and dried. (7.5 g., 94% of theory) M.P. 290-295°, with frothing. The product was recrystallised, using charcoal, from ethanol to yield cream needles, m.p. 311-312° (decomp.) of 9-chloro-4-hydroxy-3-carbethoxy-p-phenanthroline.

(Found: C, 59.5; H, 3.7; N, 9.6.

$C_{15}H_{11}O_3N_2Cl$ requires C, 59.5; H, 3.6; N, 9.3%).

This ester is soluble in moderately strong hydrochloric acid; insoluble in water, alkali and benzene, light petroleum 100/120° in the cold.

9-CHLORO-4-HYDROXY-3-CARBOXY-p-PHENANTHROLINE.

9-chloro-4-hydroxy-3-carbethoxy-p-phenanthroline (7.5 g.) m.p. 290-5° (decomp.) was refluxed for 6 hours on a water-bath with 20% methanolic potassium hydroxide (100 c.c.). During the heating, gelatinous material separated and after five hours water (in all 30 c.c.) was added as necessary to keep the solid in solution. The reddish-brown solution was boiled in an open flask with a little charcoal for 5 minutes, the charcoal removed by filtration and the pH of the solution adjusted to 4 by the addition of glacial acetic acid. After standing for 12 hours, the deposited solid was collected, drained, washed with a little fresh water and dried at 70° to yield a cream-yellow product (6.5 g., 97% of theory) M.P. 310-315°, with frothing.

Two methods of purification of the crude acid were utilised:-

(a) the yellow solid was dissolved in the minimum quantity of dilute ammonia (2N), the solution treated with a little charcoal, and dilute acetic acid (2N) added till no further acid precipitated. The collected solid was drained, washed with fresh water and dried. This procedure was carried out three times in all.

(b) the yellow solid was recrystallised, using

charcoal, from a large volume of glacial acetic acid.

The product from (a) was a very light brown material, m.p. 315-316° with frothing. Method (b) yielded white fibrous needles, m.p. 319-320° with frothing, of 9-chloro-4-hydroxy-3-carboxy-p-phenanthroline.

(Found: C, 53.3; H, 3.2; N, 9.4.

$C_{13}H_7O_3N_2Cl$, H_2O requires C, 53.3; H, 3.1; N, 9.6%).

This acid was insoluble in most of the common organic solvents. Addition of a drop of ferric chloride solution to an aqueous solution of the acid gave no colouration.

9-CHLORO-4-HYDROXY-p-PHENANTHROLINE.

(cf. KERMACK and WEATHERHEAD, J.C.S., 1940, 1164.)

METHOD A.

9-chloro-4-hydroxy-3-carboxy-p-phenanthroline (6.5 g.), m.p. 310-315° with frothing, mixed with copper-barium-chromite catalyst (0.05 g.), was added to dry, redistilled quinoline (130 c.c.) and the mixture refluxed for 40 minutes. It is important that the acid should not be contaminated with any alkali salt as this does not only fail to be decarboxylated but also inhibits the reaction, as mentioned in the theoretical discussion. The solution, cooled to 100-140°, was filtered to remove the catalyst and then further cooled to room temperature. The quinoline solution was diluted with dry diethyl ether (500 c.c.) and allowed to stand for 15 minutes. The deposited brown solid was collected, drained, washed liberally with fresh ether to remove all traces of quinoline and dried (4.5 g.) (83% of theory) m.p. 325°.

It was found possible to use less ether by concentrating the quinoline filtrate in a vacuum, but although the yield remained substantially the same the quality of the crude product was slightly inferior.

METHOD B.

9-chloro-4-hydroxy-3-carboxy-p-phenanthroline (0.4 g.) m.p. 310-315° with frothing, was placed in a dry test-tube and heated in an oil-bath. It was noticed that as the temperature rose the acid, even well-dried specimens, appeared to lose water around 280°. This water condensed on the colder upper part of the tube and was removed by wiping with filter paper. When the temperature reached 310° the solid frothed up leaving a brownish-black syrup which immediately solidified and white sublimate was observed to form on the wall of the tube. The tube was immediately withdrawn from the oil-bath and the solid removed from the tube (0.3 g.) m.p. 320-325°.

Instead of using an oil bath the tube may be carefully heated with a small flame until the frothing ceased.

The product, from either Method A or B, was suspended in dilute sodium carbonate solution (2N), any lumps being broken up to a fine state, stirred for a few minutes and collected, drained, washed thoroughly with small portions of fresh cold water to remove all traces of alkali and dried.

This product could not be conveniently crystallised from any of the common organic solvents

and was but sparingly soluble in boiling water. The method of purification adopted was to extract the crude solid with boiling water 6 or 7 times (100 c.c. portions for a 6 g. lot) and to concentrate the combined extracts to 30-50 c.c. The yellowish solid which separated was collected, drained, washed with a little fresh cold water and dried, m.p. 338-340°. This process was carried out three times to obtain yellow needles, m.p. 338-340°, of 9-chloro-4-hydroxy-p-phenanthroline.

(Found: C, 57.7; H, 3.5; N, 11.1.

$C_{12}H_7ON_2Cl, H_2O$ requires C, 57.9; H, 3.6; N, 11.3%).

This compound is soluble in dilute mineral acid and alkali, very sparingly soluble in cold water and insoluble in ethanol, acetone, ether and benzene. No colouration was obtained with ferric chloride solution on addition to a solution in dilute hydrochloric acid.

4:9-DICHLORO-p-PHENANTHROLINE.

(cf. KERMACK and WEATHERHEAD, J.C.S., 1940, 1164.)

9-chloro-4-hydroxy-p-phenanthroline (4 g.), m.p. 325°, phosphorus pentachloride (4 g.) and phosphoryl chloride (40 c.c.) were heated under reflux in an oil bath for four hours at 140°, the solid dissolving completely. The excess phosphoryl chloride was removed at 100° under reduced pressure to leave a brownish syrup which was treated with ice water to decompose any residual phosphoryl chloride. The dark solution was treated with charcoal and made alkaline with sodium carbonate solution (2N) to deposit a greyish syrup which solidified on scraping and standing for a few minutes. The greyish white solid was collected, washed with water and dried (4 g. 93 % of theory), m.p. 225-226°. Recrystallisation from ethanol yielded cream needles, m.p. 237-238°, of 4:9-dichloro-p-phenanthroline.

(Found: C, 57.6; H, 2.8; N, 11.1.

$C_{12}H_6N_2Cl$ requires C, 57.8; H, 2.4; N, 11.25%).

This compound is soluble in moderately strong hydrochloric acid, insoluble in cold water and alkali; sparingly soluble in cold benzene and light petroleum 100/120°, but soluble in these solvents on warming.

In an experiment in which 10N-sodium hydroxide solution was used instead of 2N-sodium carbonate solution to precipitate the dichloro-compound it was found that the product consisted mainly of 9-chloro-4-hydroxy-p-phenanthroline.

2 - (2-DIETHYLAMINOETHYLAMINO) - p-PHENANTHROLINE.

Diethylaminoethylamine (1 c.c.) and 2-chloro-p-phenanthroline (0.4 g.) were heated under reflux at 140° for three hours. The excess diethylamino-ethylamine was removed at 100° under reduced pressure to yield a solid yellow residue; this was dissolved in the minimum quantity of ethanol, and a few drops of ethanolic hydrobromic acid added followed by a few drops of acetone to afford cream material which after two recrystallisations from methanol formed cream platelets (0.3 g., 33% of theory) M.P. 284-285° of the tri-hydrobromide of 2 - (2-diethylaminoethyl-amino) - p-phenanthroline.

(Found: C, 40.0; H, 5.0. $C_{18}H_{22}N_4$, 3 HBr requires C, 40.2; H, 4.65%).

This salt is very soluble in cold water. The addition of alkali to the aqueous solution precipi-tates an oil which does not solidify.

2 - (3-DIETHYLAMINOPROPYLAMINO) - p-PHENANTHROLINE.

3 - Diethylaminoethylamine (1 c.c.) was added to 2 - chloro-p-phenanthroline (0.5 g.) and the mixture refluxed gently at 160° for 2 hours. The excess diethylaminopropylamine was removed in a vacuum and the white solid residue was dissolved in the minimum quantity of ethanol. The addition of a few drops of ethanolic hydrobromic acid afforded a pale yellow solid which on recrystallisation three times from methanol yielded pale yellow platelets (0.3 g.) M.P. 268-270° of the trishydrobromide of 2 - (3-diethylaminopropylamino) - p-phenanthroline. (Found: C, 39.9; H, 4.9; N, 9.8. $C_{19}H_{24}N_4$, 3 HBr, H_2O requires C, 40.1; H, 5.1; N, 9.8%).

This salt is easily soluble in water, moderately soluble in ethanol and insoluble in ether in the cold. The addition of sodium hydroxide solution to an aqueous solution precipitates an oil which solidifies to a hygroscopic solid.

2 - (4-DIETHYLAMINO-1-METHYLBUTYLAMINO) - p-PHENANTHROLINE.

2-Amino-5-diethylaminopentane (0.4 c.c.) and 2-chloro-p-phenanthroline (0.2 g.) were heated under reflux at 180° for five hours. The excess of amine was removed under reduced pressure and the residual brown-black syrup dissolved in the minimum quantity of ethanol. An ethanolic solution of picric acid (5 c.c. saturated solution) was added and the mixture refluxed for a few minutes and allowed to crystallise. Yellow material, M.P. 100-119°, was deposited. Attempts to purify this material by crystallisation from any of the common organic solvents were unsuccessful. It was suspended in a little water and 2-N-sodium hydroxide solution added till alkaline to litmus and extracted with chloroform. Removal of the solvent left an oil which was dissolved in ethanol and a few drops of a saturated ethanolic solution of 3:5 - dinitrobenzoic acid added. A brown oil was deposited which solidified on standing for two weeks. The collected brownish solid was recrystallised five times from ethanol to give yellow needles, M.P. 93-94°, of the tris-3:5-dinitrobenzoate of 2 - (4-diethyl-1-m butyl aminoethylamino) - p-phenanthroline.

(Found: C, 51.8; 52.4; H, 4.8, 4.7; N, 14.1.

$C_{21}H_{28}N_4$, $3C_7H_4O_6N_2$, C_2H_5OH requires C, 52.0; H,4.5; N, 13.7%).

This salt is soluble in ethanol and methanol in the cold, and in warm water.

4-(4-DIETHYLAMINO-1-METHYL BUTYLAMINO)-p-PHENANTHROLINE.

4-chloro-p-phenanthroline (1.4 g.) m.p. 145-6°, was mixed with re-distilled 2-amino-5-diethylaminopentane (3 c.c.), a trace of copper powder and a small crystal of iodine and heated under reflux for 5 hours at 180°. The excess amine was removed in a vacuum and the syrupy residue dissolved in water (10 c.c.) with the addition of a few drops of 2N-hydrochloric acid. The solution was filtered, rendered alkaline with dilute ammonia (2N) and extracted with ether. The extract was dried over anhydrous potassium carbonate for 6 hours and the solvent removed to yield a brown oil which was dissolved in the minimum quantity of ethanol and a saturated ethanolic solution of 3:5-dinitrobenzoic acid added till no further oil was deposited. This product on scraping and standing for a few hours solidified, was collected, drained and dried (5 g., 79% of theory), m.p. 120-125°. Recrystallisation three times from ethanol yielded yellow needles, m.p. 160-161°, loses solvent about 125°, of the tris-3:5-dinitrobenzoate of 4-(4-diethylamino-1-methylbutylamino)-p-phenanthroline.

(Found: C, 52.3; H, 4.3; N, 13.8.
$C_{21}H_{28}N_4$, $3C_7H_4O_6N_2$, $1C_2H_5OH$ requires
C, 51.9; H, 4.5; N, 13.75%).

This salt is soluble in hot water; insoluble in hot and cold benzene.

9-CHLORO-3-DIETHYLAMINOPROPYLAMINO-p-PHENANTHROLINE.

Diethylaminopropylamine (62 c.c.) and 4:9-dichloro-p-phenanthroline (3.1 g.) were heated under reflux for 6 hours at 160-170°. The excess amine was removed in a vacuum and the residual syrup was dissolved in 2N-hydrochloric acid. The solution was filtered, rendered alkaline with dilute ammonia (2N) and extracted with ether. The extract was dried over anhydrous potassium carbonate for 6 hours and the solvent removed to yield a brown oil which was dissolved in the minimum quantity of ethanol and a saturated ethanolic solution of 3:5 dinitrobenzoic acid added till no further precipitate formed. The deposited yellow solid (9 g.) was collected and recrystallised from ethanol three times to yield yellow needles, m.p. 193-194°, of the bis-3:5-dinitrobenzoate of 9-chloro-4-diethylaminopropylamino-p-phenanthroline. (Found: C, 51.75; H, 4.0; N, 14.3. $C_{19}H_{23}N_4Cl, 2C_7H_4O_6N_2$ requires C, 51.7; H, 4.1; N, 14.6%).

This salt is sparingly soluble in cold water, soluble in warm water.

A sodium fusion test for halogen carried out on the bis-3:5-dinitrobenzoate gave a positive result for chlorine.

IV. SUMMARY.

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1. From the action of Perbenzoic Acid on p-phenanthroline two products have been obtained, the mono-N-oxide and the di-N-oxide of p-phenanthroline.

2. By the action of phosphoryl chloride on these oxides, 2-chloro- and 2:7-dichloro-p-phenanthroline have been obtained.

The position of the chlorine atoms in these chloro-derivatives has been ascertained as a result of their independent synthesis by methods which are unambiguous.

3. 4-chloro- and 4:9-dichloro-p-phenanthroline have been synthesised from 6-amino-quinoline and 6-amino-8-chloro-quinoline respectively by the ethoxy-methylenemalonate method.

4. From p-phenylene diamine and ethoxymethylene-malonate, the synthesis has been achieved of 4:5-Dihydroxy- and 4:5-Dichloro-p-phenanthroline.

5. Various chloro-p-phenanthrolines have been condensed with various diethylamino-alkylamines so as to obtain p-phenanthroline derivatives carrying a basic side-chain in position 2 or 4. Amongst the compounds synthesised in this way are the following. 2-(2-diethylaminolthylamino)-, 2-(3-diethylpropylamino)-, 2-(4-diethylamino-1-methylbutylamino)-, 4-(4-diethylamino-1-methylentylamino)-, 9-chloro-4-(3-diethylamino-propylamino)-p-phenanthroline.

A note on the synthesis of 2-methyl-benzthiazole and derivatives.

It was desired to have certain derivatives of 2-methyl-benzthiazole tested for anti-filarial activity in the cotton rat. Thus it was necessary to obtain 2-methyl-benzthiazole in reasonable quantity.

Most of the earlier syntheses recorded in the literature appear to give rather poor yields of the 2-methyl-benzthiazole, thus the method of Jacobson (BER., 19, 1072) in which thioacetanilide is oxidised with alkaline potassium ferricyanide gives a yield of 20%. The method of Hofmann (BER., 13, 21) who heated 2-amino-thiophenol and acetyl chloride or acetic anhydride at 150° in a sealed tube has the disadvantage of requiring the preliminary preparation of 2-amino-thiophenol which gives a poor yield due to the instability of the 2-amino-thiophenol. An improved method of preparation of benzthiazole and its 2-alkyl-derivatives based on the method of Hofmann (BER., 12, 2362 (1879)) was recorded by Kiprianov et al. (J. Gen. Chem. (U.S.S.R.), 6, 232-235 (1936)). In this method di-o-nitrophenyl disulphide is prepared by the action of sodium disulphide on o-chloronitrobenzene. This disulphide is reduced

in glacial acetic acid with zinc dust and concentrated hydrochloric acid for one hour, the zinc salt of the o-aminothiophenol being precipated by the addition of sodium acetate in 90% yield. The benzthiazole derivative was then obtained by refluxing the zinc salt with the appropriate acid; the 2-alkyl-benzthiazole is separated from the basified solution by steam distillation. A further modification was to carry out the reduction and acylation in one operation by refluxing the reaction mixture from the reduction of the di-o-nitrophenyl disulphide with a suitable acid anhydride and benzene for several hours. In the case of 2-methyl-benzthiazole a yield of 81% of theory was reported from an experiment using 5 g. of the disulphide, reducing in glacial acetic acid with zinc dust and concentrated hydrochloric acid and refluxing with acetic anhydride and benzene for three hours.

In order to investigate the practicability of this method, di-o-nitrophenyl disulphide has been prepared smoothly and in 64% yield by the method of Bogert and Stull (Org. Syn. Coll. Vol.I. (1st Edn.) p.215). Reduction of the disulphide was carried out in glacial acetic acid on the boiling water-bath by the addition of zinc dust and concentrated hydrochloric acid in small alternate portions until the

yellow colour of the solution was completely discharged. It was found that if reduction was stopped before the discharge of this yellow colour only a trace of the 2-methyl-benzthiazole was eventually obtained. The reaction mixture from the reduction was refluxed with acetic anhydride and benzene for three hours, the benzene layer was removed under reduced pressure and the resulting solution was made alkaline with 10N-sodium hydroxide solution and steam-distilled. The product from the steam-distillation was a colourless oil which rapidly became light-brown in colour.

In a preparation using 5 g. of disulphide the yield of 2-methyl-benzthiazole was 85% of theory. When the scale of working was stepped up to 20 g. a yield of 58% of theory was obtained and on the 40 g. scale a yield of 19·2 g. of 2-methyl-benzthiazole was obtained, 51% of theory.

The methosulphate of 2-methyl-benzthiazole was prepared by the method of Browning et al. (Proc. Roy. Soc., 108, B, 126 (1931)). An attempt was made to isolate the solid methosulphate resulting from heating 2-methyl-benzthiazole with dimethyl sulphate but it was found to be hygroscopic. The solid

therefore was converted into the methochloride. The methochloride crystallised from an ethanol/ether mixture in white fibrous needles and had melting-point 247-248°; as this constant was not stated in the paper by Browning et al. (loc.cit.) this compound was submitted for analysis which confirmed that it was the methochloride of 2-methyl-benzthiazole.

The nitration of 2-methyl-benzthiazole was carried out by Browning et al. (loc.cit.) who obtained a mono-nitro substituted 2-methyl-benzthiazole, m.p. 166-167°, whose orientation was not decided. Brooker, Keyes and Williams (J.A.C.S., 64, 207 (1942)) obtained a mono-nitro-2-methyl-benzthiazole, m.p. 166-167° by nitrating in a manner essentially the same as the method used by Browning and co-workers. Brooker et al. proved the nitration product to be 6-nitro-2-methyl-benzthiazole by reducing with sodium hydrosulphite to the amino-derivative and by converting to the corresponding chloro-compound by a Sandmeyer reaction. This chloro-compound proved to be identical (m.p. and mixed m.p.) with an authentic specimen of 6-chloro-2-methyl-benzthiazole (Beilenson and Hamer, J.C.S., 1225 (1936)). In the nitration of quinazoline (Schofield and Swain, Nat., 161, 690 (1948)) it is stated that the 6-nitro-derivative is obtained and in the nitration of

acridine the 3-nitro-derivative is obtained, it is therefore interesting that 2-methyl-benzthiazole also nitrates para to the basic nitrogen atom. This probably indicates that these compounds nitrate not as the salt but as the free base, since the salt would tend to nitrate in a position meta to the quaternary nitrogen.

In the present work the method of Browning et al. (loc.cit.) has now been used for the preparation of 6-nitro-2-methyl-benzthiazole and a yield of 65% of theory was obtained by treating 2-methyl-benzthiazole in concentrated sulphuric acid with a mixture of concentrated nitric and sulphuric acids at a temperature below 10° and allowing to stand at room temperature for ½ hour.

The compounds which it was desired to test for anti-filarial activity were of two series, of styryl benzthiazole derivatives, one derived from a substituted benzthiazole base and the other from a substituted benzthiazole quaternary salt.

It was found necessary in the preparation of the styryl derivatives from the substituted benzthiazole quaternary salts to add a drop of piperidine as catalyst. In the case of the experiments using the free base of the benzthiazole derivative it was

necessary to add also a trace of hydrochloric acid. Examples of these two methods are shown in the Experimental descriptions which follow for the preparations of 2-p-nitrostyryl-benzthiazole methochloride and 2-p-dimethylaminostyryl-6-nitro-benzthiazole.

Di-o-nitrophenyl Disulphide.

(cf. Bogert, Org. Syn., Coll. Vol.I., p.215.)

Crystalline sodium sulphide (120 g.) was dissolved in 95% ethanol (500 c.c.) by heating on the water-bath. Sulphur (16 g.) was added to the hot solution and the heating continued until the sulphur had completely dissolved. This solution was added as rapidly as convenient to a solution of o-chloronitrobenzene (105 g.) dissolved in 95% ethanol (166 c.c.) and, the mixture heated under reflux on the boiling water-bath for two hours. During the period of heating, solid separated. On cooling the reaction mixture, a further amount of yellow crystals was obtained. The collected solid was drained and suspended in cold water (100 c.c.) to remove inorganic salts. The insoluble yellow solid were collected, drained and washed with cold ethanol (40 c.c.) to remove any unchanged o-chloronitrobenzene and dried to give yellow needles (65 g., 64% of theory), m.p. 195-196° of di-o-nitrophenyl disulphide.

2-Methyl-benzthiazole.

(cf. Kiprianov, Smitnik and Grigor'eva, J. Gen. Chem. (U.S.S.R.), 6, 232-235 (1936); C.A., 1936, 30, 4859.)

Di-o-nitrophenyl disulphide (40 g., m.p. 195-196°) was suspended in glacial acetic acid (240 c.c.) on the boiling water-bath. ~~Atemate~~ Portions of zinc dust (64 g.) and concentrated hydrochloric acid (160 c.c.) were added alternately in small portions as rapidly as convenient and the mixture kept on the boiling water-bath until the yellow colour of the solution was completely discharged. If the heating was discontinued before the loss of colour was attained, the yield was greatly reduced. Acetic anhydride (80 g.) and benzene (160 c.c.) were then added to the cooled solution and the mixture refluxed for three hours. The benzene was removed under reduced pressure and the solution made alkaline with 10N-sodium hydroxide solution to liberate an oil, which was purified by steam-distillation. The resulting aqueous suspension of the oil was extracted with ether and dried over anhydrous potassium carbonate. Removal of the solvent yielded a light brown oil which was redistilled at 140°/20mm. to give a colourless oil (19.2 g., 51% of theory). 2-methyl-benzthiazole was found to distil at 240° under reduced pressure. The following boiling-points are given in the literature 238° (Hofmann) and 238-240° (Jacobson).

6-Nitro-2-methyl-benzthiazole.

(cf. Browning, et al., Proc. Roy. Soc. Lond., 108, B, 119 (1924)).

2-Methyl-benzthiazole (15 g.) was mixed with concentrated sulphuric acid (45 c.c.) with efficient cooling, and the temperature adjusted to below 5° by a surrounding ice-salt mixture. To this solution was added in small portions a mixture of concentrated nitric acid (15 c.c. S.G. 1.42) and concentrated sulphuric acid (15 c.c.) the temperature being kept below 10°. After the addition was completed, the reaction mixture was allowed to stand at room temperature for ½ hour, and then poured on to ice. The separated sulphate was collected, drained, mixed into a cream with water and converted to base by the addition of ammonia until the solution was alkaline. The base was collected, drained and dried to yield a cream solid which was extracted with hot ethanol and allowed to crystallise to yield cream needles (12.6 g., 65% of theory), m.p. 166-167° of 6-nitro-2-methyl-benzthiazole.

2-Methyl-Benzthiazole Methochloride.

(cf. Browning et al. (loc.cit.)).

2-Methyl-benzthiazole (6 g.) was mixed with redistilled dimethyl sulphate (4 c.c.) and heated on the warm water-bath until a moderately vigorous reaction set in, and the mixture solidified. The solid methosulphate was dissolved in water (10 c.c.), 10N-hydrochloric acid (5 c.c.) added and the solution boiled for a few minutes. Barium chloride solution (containing 15·2 g. $BaCl_2H_2O$/250 c.c. water) was added until no further precipitate formed and the solution digested on the water-bath for 30 minutes. The suspended barium sulphate was removed by filtration and the filtrate taken to dryness on the water-bath. The solid residue was extracted with hot ethanol which yielded on cooling white needles (6 g., 75% of theory). Recrystallisation from an ethanol/ether mixture yielded white fibrous needles m.p. 247-248° of 2-methyl-benzthiazole methochloride. (Found: N, 5·9. Calc. for $C_{19}H_{10}NSCl,1C_2H_5OH$: N, 5·7%)

6-Nitro-2-methyl-benzthiazole methochloride.

2-Methyl-6-nitro-benzthiazole (6·4 g.) and re-distilled dimethyl sulphate (4·2 g.) were heated at 100° in nitrobenzene (25 c.c.) for two hours. During the heating greenish plates separated and on cooling a further quantity of product was obtained. The collected solid was drained well, washed with a little benzene followed by ether and dried to give a whitish-green product (6·3 g.), m.p. 195-200°. On diluting the filtrate with benzene a further quantity of product was obtained (2 g.) m.p. 194-198°.

The combined quantities of methosulphate were dissolved in water (50 c.c.), concentrated hydro-chloric acid (5 c.c.) added, and the solution boiled for 15 minutes. Barium chloride solution (containing 15·2 g. $BaCl_2H_2O$/250 c.c. H_2O) was added till no further precipitate formed and the boiling continued for one hour. The cooled solution was filtered and the filtrate taken to dryness. The white solid residue was extracted with hot ethanol. The cooled extract was diluted with a little diethyl ether to deposit a white product (6 g., 86% of theory). Recrystallisation from an ethanol/ether mixture yielded white needles, m.p. 232-233°, which analysis confirmed as being 2-methyl-6-nitrobenzthiazole

methochloride.

(Found: N, 10·4. $C_9H_9O_2N_2SCl,\frac{1}{2}C_2H_5OH$ requires N, 10·5%).

2-p-Nitrostyryl-benzthiazole methochloride.

2-Methyl-benzthiazole methochloride (0.4 g.) was dissolved in ethanol (20 c.c.) and p-nitrobenzaldehyde (0.3 g.) added. When solution was complete, a drop of piperidine was added as catalyst causing a brown colour to develop and after a few minutes a cream solid separated. The mixture was refluxed on the water-bath for ten hours. On cooling, the separated solid was collected, drained and dried in a vacuum (0.5 g.). Recrystallisation from water yielded golden fibrous needles, m.p. 228-229°, which analysis proved to be 2-p-nitrostyryl-benzthiazole methochloride. (Found: C, 54.5; H, 4.3; N, 7.9. $C_{16}H_{13}O_2N_2SCl.1H_2O$ requires C, 54.8; H, 4.3; N, 8.0%).

2-p-Dimethylaminostyryl-6-nitro-benzthiazole.

6-Nitro-2-methyl-benzthiazole (1 g.) and p-dimethyl-amino-benzal-dehyde (0·8 g.) were refluxed in ethanol (30 c.c.) with a drop of piperidine and a drop of ethanolic hydrochloric acid as catalysts for three hours. On cooling crystals separated from the purple-coloured solution, and were collected, drained and dried (0·5 g.). The product was extracted with hot ethanol to remove unchanged 6-nitro-2-methyl-benzthiazole, and the insoluble red solid was recrystallised from benzene in purple needles, m.p. 261-262° which analysis proved to be 2-p-dimethylaminostyryl-6-nitro-benzthiazole. (Found: C, 60·9; H, 4·5; N, 12·3. $C_{17}H_{15}O_2N_3S.\frac{1}{2}H_2O$ requires C, 61·1; H, 4·8; N, 12·6%).

This compound is soluble in strong hydrochloric acid and insoluble in water. On dilution of the solution in strong acid with the base is obtained. It is soluble in benzene showing a yellow-green fluorescence.

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